Written Testimony of Richard H. Ebright

Board of Governors Professor of Chemistry and Chemical Biology, Rutgers University

Laboratory Director, Waksman Institute of Microbiology

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Subcommittee on Emerging Threats and Spending Oversight

For the Hearing "Origins of COVID-19: An Examination of Available Evidence"

June 18, 2024

Chair Peters, Ranking Member Paul, and members of the Committee:

Thank you for inviting me to discuss the origins of COVID-19. I am Board of Governors Professor of Chemistry and Chemical Biology at Rutgers, The State University of New Jersey, and Laboratory Director at the Waksman Institute of Microbiology. I direct a biomedical research laboratory and serve as project leader on two National Institutes of Health (NIH) research grants. I conduct research on the mechanism of bacterial RNA synthesis and on the development of new antibacterial therapeutic agents able to treat bacterial infections resistant to current drugs. My research involves both priority public health bacterial pathogens (e.g., the pathogens responsible for Staph infections, Strep infections, and tuberculosis) and priority biodefense bacterial pathogens (e.g., the pathogens responsible for anthrax, plague, and tularemia). I am a member of the Institutional Biosafety Committee of Rutgers University and a co-founder of Biosafety Now, and I have been a member of the Working Group on Pathogen Security of the state of New Jersey, the Controlling Dangerous Pathogens Project of the Center for International Security Studies, and the Biosecurity Advisory Board of the Center for Civilian Biodefense. Here, I discuss the origin of COVID-19. In my written comments, I also include an appendices addressing the fact that lapses in US oversight of gain-of-function research and enhanced potential pandemic pathogen research likely contributed to the origin of COVID-19 and providing the official, legally controlling, US-government definitions of gain-of-function research and enhanced potential pandemic pathogen research. My assessments are based on information in published NIH, Health and Human Services (HHS), Office of Science and Technology Policy (OSTP), and Congressional Research Service (CRS) documents, on published press reports, on published scientific papers, and on my knowledge of biosafety and biosecurity standards for work with pathogens.

Conclusion

A large preponderance of evidence indicates that COVID-19 has a human origin, rather than a natural origin, with SARS-CoV-2, the virus that causes COVID-19, having entered humans through a research-related incident.

This conclusion is based on information in publicly available documents, press reports, and scientific papers; on my research experience in microbial genomics, microbial genetics, DNA-synthesis technology, and recombinant-DNA technology; and on my knowledge of and experience with biosafety, biosecurity, and biorisk-management standards for work with pathogens.

Evidence

Key facts and data supporting this conclusion are as follows:

1. Location of emergence of COVID-19: Wuhan

COVID-19 emerged in late 2019 in Wuhan, China (1-2). COVID-19 is caused by SARS-CoV-2, a virus that is closely similar to bat SARS-related coronaviruses and that was first isolated in late 2019 in Wuhan China (3-6).

Wuhan, a city of 11 million, is located 800 miles from the closest colonies of bats that harbor SARS-CoV-2-related coronaviruses (Yunnan province, China; 7) and is located outside the flight range of bats that harbor SARS-CoV-2-related coronaviruses (8-9). The large distance between Wuhan and bats harboring possible precursors of SARS-CoV-2 argues against natural spillover from bats to humans--with or without an animal intermediate--in Wuhan. The large distance,

together with the absence of reported human infections or animal infections earlier in 2019 in any closer location, argues against natural spillover from bats to humans--with or without an animal intermediate--earlier in 2019 in any location.

Wuhan is the location of laboratories that, in 2019, were conducting the largest research program on bat SARS-related coronaviruses on the planet: Wuhan Institute of Virology, Wuhan University, and Wuhan Center for Disease Control (10). Wuhan is the location of laboratories that, in 2015 and 2017, had been singled out by scientists and science-policy specialists as conducting and contemplating research that posed an unacceptably high risk of a laboratory accident that could trigger a pandemic (11-13); that, in 2019, possessed the largest collection of bat SARS-related coronaviruses on the planet (14-15); and that, in 2019, possessed the full genome sequence of RaTG13, the bat SARS-related coronavirus identified before the outbreak that was the most closely similar to SARS-CoV-2 on the planet (collected by Wuhan Institute of Virology in 2013 from a bat colony in a mine in which miners had died of SARS-like pneumonias; partly sequenced in 2013-2016; fully sequenced in 2018; 3, 16-17).

The match between the global epicenter of COVID-19 emergence and the global epicenter of high-risk research on bat SARS-related coronaviruses argues strongly for the possibility that SARS-CoV-2 entered humans though a research-related incident.

2. Wuhan research on SARS-related coronaviruses

The Wuhan Institute of Virology, Wuhan University, and Wuhan Center for Disease Control performed high-risk virus discovery research on bat SARS-related coronaviruses in 2013-2019 (10, 16, 18-21), and the Wuhan Institute of Virology and Wuhan University performed extremely-high-risk gain-of-function research and enhanced potential pandemic pathogen

research on bat SARS-related coronaviruses in 2015-2019 (10, 20, 22-24). The term "gain-of-function research" in this context refers to research reasonably anticipated to increase the transmissibility and/or pathogenicity of a pathogen (definition in US-government policy in effect in 2014-2017; 25). The term "enhanced potential pandemic pathogen research" in this context refers to research reasonably anticipated to increase the transmissibility and/or virulence of a potential pandemic pathogen (definition in US-government policy in effect in 2018-present; 26).

In the Wuhan researchers' virus discovery research, the researchers searched for new bat SARS-related coronaviruses in caves and mineshafts in remote rural areas in Yunnan province, brought samples of new bat SARS-related coronaviruses to Wuhan, and then sequenced, cultured, and characterized new bat SARS-related coronaviruses year-round in Wuhan (10, 16, 18-21).

In the Wuhan researchers' gain-of-function research and enhanced potential pandemic pathogen research, the researchers genetically modified bat SARS-related coronaviruses, constructing and characterizing novel viruses that had enhanced ability to infect and replicate in human cells and that had enhanced viral growth and enhanced lethality in mice engineered to possess human receptors for SARS viruses ("humanized mice"; 10, 20, 22-24).

In 2015-2017, scientists and science-policy specialists expressed concern that the Wuhan Institute of Virology was conducting and contemplating research that posed an unacceptably high risk of a laboratory accident and pandemic (11-13). At a November 2015 Royal Society/National Academies meeting on "Gain of Function and Options for Regulation" at Chicheley Hall, UK, the research project on SARS-related coronaviruses then being carried out jointly by the Wuhan Institute of Virology and the University of North Carolina at Chapel Hill was singled out as the project most likely--of all projects in the world--to trigger a pandemic

(12).

In 2017-2018, with NIH funding, the Wuhan Institute of Virology constructed novel "chimeric" (hybrid) SARS-like coronaviruses that combined the "spike genes" (the genes that govern host-specificity, infectivity, and immunogenicity of coronaviruses)--from uncharacterized new bat SARS-related coronaviruses with the rest of the genetic information from other bat SARS-related coronaviruses, obtaining viruses that efficiently infected and replicated in human airway cells (20, 22-24), and obtaining at least one novel chimeric virus that had *10,000x enhanced viral growth in lungs, 1,000,000x enhanced viral growth in brains, and 3x enhanced lethality* in humanized mice (22-24, 27-29). The observed 10,000x to 1,000,000x enhancements of viral growth are remarkably high enhancements of viral growth. In 2016, the NIH had written to the grantee, and had added text to the Terms and Conditions of the grant, stating that construction of a virus having a 10x or higher enhancement of viral growth would necessitate stopping research and immediately notifying the NIH (22, 27-29). However, despite exceeding--by a factor of 1,000--the threshold for stopping research and immediately notifying the NIH, the researchers did not stop research and did not immediately notify the NIH (27-31).

In 2018--just one year before the pandemic--in an NIH grant proposal, the Wuhan Institute of Virology and its collaborators proposed to construct additional novel chimeric SARS-related coronaviruses, proposing to construct chimeras that possessed spikes having higher binding affinities for human SARS receptors, and hypothesizing that chimeras that possessed spikes having higher binding affinities for human cells would have enhanced pandemic potential (22).

Also in 2018--just one year before the pandemic--in a Defense Advanced Research Projects Agency (DARPA) grant proposal, the Wuhan Institute of Virology and collaborators proposed

(i) to construct additional novel chimeric SARS-like coronaviruses, (ii) to construct novel "consensus" SARS-related coronaviruses, (iii) to construct novel chimeric and consensus SARS-related coronaviruses having a furin cleavage site (FCS)--a feature associated with increased viral growth and increased transmissibility--inserted at the spike S1-S2 border, and (iv) to construct these novel viruses by synthesizing six nucleic-acid building blocks assembling the six synthetic nucleic-acid building blocks using the reagent BsmBI (a Type-IIS restriction endonuclease that enables seamless and non-seamless directional cloning for genome assembly) (32-33).

[A "consensus" sequence--a sequence obtained by aligning known examples of functional sequences and identifying the most common residue at each position in the alignment--typically defines the most highly functional sequence of all possible sequences (i.e., the "ideal" or "golden-mean" functional sequence, which no or few natural functional sequences match perfectly, but which all natural functional sequences approximate; 34). Synthesizing and characterizing, consensus sequences has been a standard experimental approach across molecular biology for four decades (34-41). In work published in 2008, one of the drafters of the 2018 DARPA proposal synthesized and characterized a consensus bat SARS-like coronavirus, and showed that this approach enables researchers to "overcome...obstacles by allowing studies of replication and pathogenesis without identification of reservoir species or cultivation of primary isolates" and thereby enables researchers to "test a possible route of emergence from the noncultivable Bat-SCoV to human SARS-CoV" (42).]

The 2018 NIH proposal was funded (43). The 2018 DARPA proposal was not funded, due to concerns expressed by reviewers about "Regulatory and ELSI [ethical, legal, and social implications] issues" and "risks of Gain of Function (GoF) and DURC [dual-use research of

concern]" (44). Because the funded NIH proposal and unfunded DARPA proposal had overlapping scope and overlapping aims, it would be permissible under NIH grant policies (45-46)--and would be the typical practice for NIH grantees--to use the funded NIH proposal to support work proposed in the unfunded DARPA proposal. Therefore, it is likely that, in 2019, researchers at the Wuhan Institute of Virology undertook *both* work proposed in the 2018 NIH proposal and work proposed in the 2018 DARPA proposal.

3. Biosafety precautions in Wuhan research on SARS-related coronaviruses

The virus-discovery research performed by the Wuhan Institute of Virology and the Wuhan Center for Disease Control routinely used biosafety standards and personal protective equipment that would pose high risk of infection of laboratory staff upon contact with a virus having the transmission properties of SARS-CoV-2 (i.e., biosafety level 2, with just gloves and lab coat as personal protective equipment; or less than biosafety level 2, with no personal protective equipment; 7, 10, 21, 47).

The gain-of-function research and enhanced potential pandemic pathogen research projects on SARS-related coronaviruses at the Wuhan Institute of Virology also routinely used biosafety standards and personal protective equipment that would pose high risk of infection of laboratory staff upon contact with a virus having the transmission properties of SARS-CoV-2 (i.e., biosafety level 2, with just gloves and lab coat as personal protective equipment; 7, 10, 47).

Laboratory accidents that result in laboratory-acquired infections and/or laboratory releases are surprisingly common, even in the US, Canada, and Europe, and even at biosafety levels higher than biosafety level 2 (48-51). In the US, in 2022, the most recent year for which data are available, 143 laboratory releases--*almost 3 per week*--resulting in occupational exposures of

Select Agents (a subset of pathogens and biological toxins regulated based on high potential for use in biological warfare, bioterrorism, or biocrime) were reported to the Federal Select Agent Program (48). In Canada, in 2016-2022 the most recent period for which data are available, 361 laboratory incidents--*almost 1 per week*--resulting in confirmed exposures of pathogens and biological toxins were reported to the Laboratory Incident Notification Canada surveillance system (49). In the UK, in 2020-2023, the most recent period for which data are available, 156 laboratory incidents--*almost 1 per week*--involving pathogens and biological toxins were recorded (50).

For context, the second, third, and fourth entries of SARS-CoV-1 into the human population occurred as a laboratory-acquired infection in Singapore in 2003 at biosafety level 3 (a higher biosafety standard than used at Wuhan Institute of Virology for research on SARS-related coronaviruses; 52), a laboratory-acquired infection in Taipei in 2003 at biosafety level 4 (a much higher biosafety standard biosafety standard than used at Wuhan Institute of Virology for research on SARS-related coronaviruses; 53), and at least two independent laboratory-acquired infections--and subsequent community transmission to at least five family members and associates of infected lab workers and at least one healthcare worker attending to an infected lab worker--in Beijing in 2004 at biosafety level 3 (a higher biosafety standard that used at Wuhan Institute of Virology for research on SARS-related coronaviruses; 54-55).

For further context, SARS-CoV-2 has caused at least two laboratory-acquired infections: in Beijing in 2020 at biosafety level 3 (56) and in Taipei in 2021 at biosafety level 3 (57).

4. Genome sequence of SARS-CoV-2

In 2019, a novel SARS-related coronavirus having a spike with extremely high binding affinity

for human SARS receptors, a furin cleavage site (FCS) at the spike S1-S2 junction, and a genome sequence with regularly spaced Type IIS restriction-endonuclease sites enabling genome assembly from six synthetic nucleic-acid building blocks--a virus having the exact features proposed in the 2018 NIH and DARPA proposals discussed in section 2--emerged on the doorstep of the Wuhan Institute of Virology (3-5).

SARS-CoV-2 is the only one of more than 800 known SARS-related coronaviruses (sarbecoviruses) that possesses an FCS (58-59). *Mathematically, this finding--by itself--implies that the probability of encountering a natural SARS-related coronavirus possessing an FCS is less than 1 in 800 ($P < 0.005$).* In conjunction with the 2018 DARPA proposal that explicitly proposed inserting an FCS at the spike S1-S2 junction of chimeric and consensus SARS-related coronaviruses, the presence of an FCS at the spike S1-S2 junction in SARS-CoV-2 provides strong support for a research-related origin (60-63).

The FCS of SARS-CoV-2 has codon usage (the pattern of preferences among synonymous three-nucleotide sequences encoding amino acids in the genetic code) that is highly unusual for a bat SARS-related coronavirus (58). The FCS of SARS-CoV-2 contains two consecutive CGG codons, where CGG is one of six synonymous codons for the amino acid arginine, and is used rarely--as less than 1 in 30 codons for arginine--in bat SARS-related coronaviruses, but is used frequently in humans (58). *Mathematically, the probability of encountering a natural SARS-related coronavirus having two consecutive CGG codons is less than 1 in 30 ($P < 0.05$; assuming non-independent codon selection for the two codon positions) to less than 1 in 9,000 ($P < 0.005$; assuming independent codon selection for the two codon positions).* In conjunction with the 2018 DARPA proposal explicitly proposing the insertion of an FCS into chimeric and consensus SARS-related coronaviruses--an insertion a genetic engineer typically would make

employing codon usage characteristic of the target organism, in this case humans--the highly unusual, non-bat-SARS-related-coronavirus-like, human-like codon usage in the FCS of SARS-CoV-2 provides strong support for a research-related origin (32-33; 60-61, 63).

The FCS of SARS-CoV-2 has an 8-of-8 amino-acid-sequence identity to the FCS of human epithelial sodium channel α (ENaCα; 64-65), an FCS that previously had been shown to be efficiently cleaved in human airway cells and that thus would be a rational, arguably the most rational, FCS for a genetic engineer to insert in a virus targeting human airway cells (65). This feature, by itself, does not rule out natural origin, but is more easily explained by a research-related origin (65).

The genome of SARS-CoV-2 has a number and pattern of spacing of Type-IIS restriction-endonuclease sites that suggests the genome was assembled from six synthetic nucleic-acid building blocks using the Type-IIS restriction endonuclease BsmBI as an assembly reagent (62). This feature, by itself, does not rule out natural origin, but is more easily explained by a research-related origin. In conjunction with the 2018 DARPA proposal explicitly proposing the construction of chimeric and consensus viruses by genome assembly from six synthetic nucleic-acid building blocks using BsmBI provides strong support for a research-related origin (32-33; 60-63).

Taken together, the presence of a spike having an extremely high affinity for human SARS receptors, the presence of an FCS at the spike S1-S2 junction, the highly unusual codon usage of the sequence encoding the FCS, the number and pattern of spacing of Type-IIS restriction-endonuclease sites, and the one-for-one match between these unusual features and the specific features proposed to be engineered into in the 2018 NIH and 2018 DARPA proposals, make an

extremely strong case--a "smoking gun"--for a research-related origin (58, 60-63, 65-66).

5. Properties of SARS-CoV-2

Three properties of SARS-CoV-2 at the time of emergence of COVID-19 suggest "pre-adaptation" to humans that differs from the pattern observed for SARS-CoV-1 and other viruses that entered humans through natural spillover (67-73).

First, as compared to SARS-CoV-1, SARS-CoV-2 showed much less early sequence divergence in the initial period after emergence, suggesting that, as compared to SARS-CoV-1, SARS-CoV-2 was better pre-adapted to humans (67).

Second, the spike from SARS-CoV-2 exhibits an extremely high binding affinity for the SARS receptor from humans (human ACE2; 68). The spike from SARS-CoV-2 binds to human ACE2 5x to 20x more tightly than the spike from SARS-CoV-1 (68). In addition, the spike from SARS-CoV-2 binds to human ACE2 more tightly than it binds to ACE2 from most other species, and, in particular, binds to human ACE2 much more tightly than it binds to ACE2 from bats (the putative reservoir species) (69-72).

Third, the SARS-CoV-2 exhibits an extremely high ability to infect and replicate in human cells (3). SARS-CoV-2 infects and replicates human cells much more efficiently that it does cells from bats (the putative reservoir species) (73).

These observations are difficult to reconcile with natural spillover directly from bats to humans, are difficult to reconcile with natural spillover from bats to an intermediate animal species to humans, but are as expected for research-related spillover involving in-laboratory pre-adaptation to humans through gain-of-function research or enhanced potential pandemic pathogen research.

6. Obstruction of investigation by Wuhan researchers

In 2019-present, the Wuhan Institute of Virology has withheld information, misrepresented facts, and obstructed investigation, even though, if not implicated in the origin of SARS-CoV-2, it could clear its name though cooperation with investigation (28-31, 74-81).

The Wuhan Institute of Virology has deactivated a database of virus sequences in fall 2019, has refused all requests for sequences of unpublished viruses, has made false statements about the number, identities, origins, and properties of viruses in its possession (28-31, 74-81).

Prior to September 2019, the Wuhan Institute of Virology maintained an online database of unpublished partial and full virus genome sequences (74-76). Access to this database could show whether Wuhan laboratories possessed unpublished sequences of bat SARS-related coronaviruses closely related to SARS-CoV-2, possibly including unpublished sequences of bat SARS-related coronaviruses more closely related than RaTG13 to SARS-CoV-2. On September 12, 2019--in the period spanning July-November 2019 in which SARS-CoV-2 first entered humans (see section 8), the Wuhan Institute of Virology deactivated its online database, and, at all subsequent times, the Wuhan Institute of Virology has refused requests, including repeated formal requests from the NIH, to reactivate the online database or to share its contents (28-31, 74-76, 79-80).

In a January 2020 scientific paper reporting the genome sequences of SARS-CoV-2 and RaTG13, and in a December 2020 addendum to the paper, the Wuhan Institute of Virology made material misstatements and material omissions that obfuscated the identity and origin of RaTG13 and the timing of the identification and sequencing of RaTG13 (3, 16-17, 77). Most notably, in their January 2020 paper, the Wuhan researchers failed to note that RaTG13 had been collected

in 2013, from a bat colony in a mine in which miners had died of SARS-like pneumonias, had been partly sequenced in 2013-2016, and had been fully sequenced in 2018. In addition, the Wuhan researchers never have satisfactorily explained the relationship between RaTG13 and the bat SARS-related coronavirus, BtCoV/499, for which a partial sequence published in 2016 (16) shows very high, but not complete, sequence similarity.

In a January 2020 scientific paper reporting the sequences of SARS-CoV-2 and RaTG13, the Wuhan Institute of Virology failed to mention--and instead obfuscated by truncating a sequence alignment--the presence of the furin cleavage site in SARS-CoV-2 and the presence of the two consecutive rare arginine codons in the sequence encoding the FCS (3, 16-17, 78). The failure to mention the furin cleavage site in the paper has been compared to describing a unicorn--describing its mane, tail, legs, and hoofs in detail--but failing to mention its horn (78).

On November 5, 2021, and again on January 6, 2022, the NIH formally requested dated copies of original laboratory notebook entries, original electronic files, and other text records relating to NIH-supported research on SARS-related coronaviruses performed by the Wuhan Institute of Virology (28-31, 79-80). The Wuhan Institute of Virology did not respond to the NIH requests, resulting in the termination of NIH funding to the Wuhan Institute of Virology on August 19, 2022, the debarment of the Wuhan Institute of Virology from participation in US-government procurement and non-procurement programs on July 17, 2023, the suspension and proposed debarment of EcoHealth Alliance from participation in US-government procurement and non-procurement programs on May 15, 2024, and the suspension and proposed debarment of EcoHealth Alliance president Peter Daszak from participation in US-government procurement and non-procurement programs on May 22, 2024 (28-31, 79-80).

7. Intelligence data

US intelligence data indicate that at least three researchers from the Wuhan Institute of Virology project on engineered SARS-related coronaviruses--project co-leader Ben Hu and project staffers Yu Ping, and Yan Zhu--sought treatment at Wuhan hospitals in November 2019 for serious lower-respiratory-tract infections with symptoms consistent with COVID-19, including ground-glass opacities on lung X-rays and loss of sense of smell (82-87).

8. Absence of evidence for natural origin

No--zero--sound evidence has been presented that SARS-CoV-2 has a natural origin. No natural reservoir host has been identified, no natural intermediate host has been identified, suggestions that SARS-CoV-2 first entered humans at the Huanan Seafood Market in Wuhan are false, and papers widely cited as providing evidence for natural origin are unsound.

- **No natural reservoir host has been found.** No natural reservoir host for SARS-CoV-2 has been identified, despite four years of intensive searching in nature using state-of-the-art nucleic-acid amplification and sequencing (78, 88). Bats have been suggested as a natural reservoir host, but no viruses having sufficient genome-sequence similarity to SARS-CoV-2 to have served, without laboratory manipulation or long adaptation in an intermediate host or in humans, have been identified in bats.

- **No natural intermediate host for SARS-CoV-2 has been identified.** No natural intermediate host for SARS-CoV-2 has been identified, and no direct evidence has been obtained for infection of any non-human animal species by SARS-CoV-2 prior to 2020, despite four years of intensive searching in nature and archived samples using state-of-the-art

nucleic-acid sequencing (78, 88). Various animals, including bats, pangolins, and raccoon dogs, have been suggested as possible natural reservoir hosts or natural intermediate hosts, but no viruses having sufficient genome-sequence similarity to SARS-CoV-2 to have served, without laboratory manipulation or long adaptation in an intermediate host or in humans, have been identified in any animal species. The failure to identify an infected natural intermediate host for SARS-CoV-2 is in striking contrast to the rapid identification of an infected natural intermediate host for SARS-CoV-1, the virus that caused the SARS outbreak of 2002-2003; in the case of SARS-CoV-1, infected intermediate hosts, palm civet cats, were identified within months and were traced directly to infected humans using the much less advanced nucleic-acid amplification and sequencing procedures available in 2002-2003 (78, 88-89).

- **Suggestions that SARS-CoV-2 entered humans at the Huanan Seafood Market are false.** Because some human cases of COVID-19 in mid- to late December 2019 were associated with the Huanan Seafood Market in Wuhan, it has been suggested that SARS-CoV-2 may first have entered humans at the Huanan Seafood Market in Wuhan (90-93).

  However this suggestion is false. *Phylogenomic evidence, epidemiological evidence, and documentary evidence all indicate that SARS-CoV-2 entered humans in July-November 2019* (1-2, 83-87, 94-102 [entry in July-November 2019 in ref. 94; entry in August 2019 in refs. 95-96; entry in September-October 2019 in ref. 97; entry in September-November 2019 in ref. 98; entry in September 2019 in ref. 99; entry in October-November in ref. 100; and entry in or before November 2019 in refs. 1-2, 83-87, and 101-102]). *Human cases at the Huanan Seafood Market in mid- to late Dec 2019 cannot--even in principle--shed light on spillover into humans that occurred one to five months earlier, in July-November 2019.*

Liu et al. 2023 performed extensive environmental sampling at the Huanan Seafood Market and found no evidence for an infected animal (103). Liu et al. 2023 suggest that the market was the location of an "amplifier" event (i.e., a super-spreader event in an outbreak that already had started elsewhere and that had been brought to the market by humans infected elsewhere; 103).

- **Arguments of Andersen et al. 2020 are unsound.** Andersen et al. 2020 states putative arguments against a laboratory origin of SARS-CoV-2 (104), concluding "Our analyses clearly show that SARS-CoV-2 is not a laboratory construct or a purposefully manipulated virus" and "we do not believe that any type of laboratory-based scenario is plausible."

  However, Andersen et al. 2020 is not a research paper (104). It presents no new data and presents no new data analyses. It is strictly an opinion piece, published as "Correspondence" (defined by the publisher as "a forum for discussion or to present a point of view" that "should not contain new research data"; 105).

  The arguments in Andersen et al. 2020 are scientifically unsound and have been disputed as being scientifically unsound (106). Cretien and Cutlip 2020, a working paper from the Defense Intelligence Agency, concluded: "The arguments that Andersen et al. use to support a natural-origin scenario for SARS-CoV-2 are based not on scientific analysis, but on unwarranted assumptions. A long line of research shows that leading coronavirus laboratories do not work as described in...Andersen et al....While key components of a laboratory effort resulting in SARS-CoV-2 have not been reported, such as generation of the furin cleavage site and development of a new reverse genetic system, this does not prove they did not occur. Coronavirus researchers have conducted these studies for other coronaviruses; technically

they would not have been difficult. The recent RaTG13 report demonstrates coronavirus researchers do not publish all of their research at the time it is conducted" (106).

In addition, compelling evidence has been presented that Andersen et al. 2020 is a product of scientific misconduct, up to and including scientific fraud (107-108). Private email and Slack communications of authors Andersen, Garry, Holmes, and Rambaut--made public through a Congressional inquiry--show that the authors knew the main conclusions of their paper were invalid at the time the paper was drafted, at the time the paper was submitted for publication, and even at the time the paper was published (107-108).

For example, in private email and Slack communications, first author Andersen wrote "the lab escape version of this is so friggin' likely to have happened because they were already doing this type of work and the molecular data is fully consistent with that scenario" on the day the first draft of the paper was started; wrote "accidental escape is in fact highly likely" and "we can’t prove one way or the other, but we never will be able to" on the next day; wrote "From a genomics perspective, the theories Richard Ebright lay out I expect would look the same - there would be no way to distinguish between them" four days later; wrote "The furin link keeps bugging me" on the day the first draft of the paper was completed; wrote "we unfortunately just can’t rule out a potential accidental infection from the lab" on the day the paper was submitted for publication; and wrote "we can’t fully disprove culture" and "We also can’t fully rule out engineering" a month after publication of the paper (107-108).

As a further example, in private email and Slack communications, author Garry wrote "I really can’t think of a plausible natural scenario where you get from the bat virus or one very

similar to it to nCoV where you insert exactly 4 amino acids, 12 nucleotides, that all have to be added at the exact same time to gain this function....I just can't figure out how this gets accomplished in nature" and "Of course, in the lab it would be easy to generate the perfect 12 base insert that you wanted" on the day the first draft of the paper was started; wrote "The major hangup I have is the polybasic cleava[g]e site....Contributing to my hangup. Its not two basic amino acids it's three plus the proline, and it's a perfect 12 base insertion - no mutations at all in the rest of $2. So this major variation occurred without any other changes anywhere close" and "Transmitting a b[a]t virus like RatG13 in HeLa cells and then asking your graduate student to insert a furin site...would get you there. It's not crackpot to suggest this could have happened given the GoF research we know is happening" on the next day; and wrote "You could put the furin site in very cleanly" and "You can also synthesize bits of the genes de novo with perfect precision then add them back in without a trace" three days later (107-108).

Formal requests for retraction of Andersen et al. 2020 for scientific misconduct have been submitted (109-110).

- **Arguments of Worobey et al. 2022 are unsound.** Worobey et al. 2022 (90), a paper authored by the four authors of Andersen et al. 2020 for whom evidence for scientific misconduct, up to and including scientific fraud, has been presented (104, 107-110; see preceding paragraph), presents a geospatial analysis that purportedly suggests SARS-CoV-2 entered humans at the Huanan Seafood Market in Wuhan.

  However, the arguments in Worobey et al. 2022 are scientifically unsound and have been disputed as being scientifically unsound (111-113). Zhang et al 2022 point out intra-market

differences in the locations of animal cages and the locations of environmental samples positive for SARS-CoV-2 that invalidate the conclusions of Worobey et al. (111). Weissman 2024 points out that ascertainment bias invalidates the conclusions of Worobey et al. (112). Stoyan and Chiu, 2024 point out that the statistical analyses in Worobey et al. are unsound (113). Furthermore, as noted above in section 8, phylogenomic evidence, epidemiological evidence, and documentary evidence all indicate that SARS-CoV-2 entered humans in July-November 2019 (1-2, 83-87, 94-102); therefore, arguments based on data for the Huanan Seafood Market on or after mid to late December 2019--as in Worobey et al. 2022--cannot, even in principle, shed light on spillover into humans that occurred in July-November, 2019.

When a paper is scientifically unsound and has four authors, including a corresponding author, who have committed scientific misconduct on a previous paper on the same subject--as for Worobey et al. 2022--there is clear basis to infer the paper may be product of scientific misconduct, up to and including fraud.

A formal request for retraction of Worobey et al. 2022 for scientific unsoundness and possible scientific misconduct, up to and including fraud, has been submitted (114).

- **Arguments of Pekar et al. 2022 are unsound.** Pekar et al. 2022 (91), a paper authored by the four authors of Andersen et al. 2020 for whom evidence for scientific misconduct, including scientific fraud, has been presented (104, 107-110; see above), presents a phylogenomic analysis that purportedly suggests SARS-CoV-2 entered humans at the Huanan Seafood Market in Wuhan.

However, the arguments in Pekar et al. 2022 are scientifically unsound and have been disputed as being scientifically unsound (115-117). Massey et al. 2023 point out that the unwarranted exclusion of intermediate sequences invalidates the conclusions of Pekar et al. (115). Lv et al. 2024 report new intermediate sequences that invalidate the conclusions of Pekar et al. (116). PubPeer comments report computational errors that invalidate--*in toto*--the conclusions of Pekar et al. (117). Furthermore, as noted above in section 8, phylogenomic evidence, epidemiological evidence, and documentary evidence all indicate that SARS-CoV-2 entered humans in July-November 2019 (1-2, 83-87, 94-102); therefore, arguments based on data for the Huanan Seafood Market on or after mid- to late December 2019--as in Pekar et al. 2022--cannot, even in principle, shed light on spillover into humans that occurred in July-November, 2019.

When a paper is scientifically unsound and has four authors, including a corresponding author, who have committed scientific misconduct on a previous paper on the same subject--as for Pekar et al. 2022--there is clear basis to infer the paper may be product of scientific misconduct, up to and including fraud.

A formal request for retraction of Pekar et al. 2022 for scientific unsoundness and possible scientific misconduct, up to and including fraud, has been submitted (114).

- **Arguments of Crits-Christoph et al. 2023a,b are unsound.** Crits-Christoph et al. 2023a and 2023b (92-93), non-peer-reviewed preprints authored by the four authors of Andersen et al. 2020 for whom evidence for scientific misconduct, including scientific fraud, has been presented (104, 107-110; see above), re-hashes the data collected by Liu et al. 2023 (103) to claim support for the hypothesis that SARS-CoV-2 entered humans at the Huanan Seafood

Market in Wuhan and for the hypothesis that raccoon dogs were the intermediate host species for spillover to humans.

However, the arguments in Crits-Christoph et al. 2023a,b are scientifically unsound and have been disputed as being scientifically unsound (118-119). Bloom, 2023a and 2023b point out that the arguments of Crits-Christoph et al. concerning raccoon dogs are invalid, being based on just 16 sequence reads (1-6 per sample) in samples containing more than 600 million sequence reads (less than 1 part in 2.7 million; a signal level far below background noise) and points out that there is a negative correlation--not a positive correlation--between sequence reads for nucleic acids from SARS-CoV-2 and sequence reads for nucleic acids from raccoon dogs (118-119). Furthermore, as noted above in section 8, phylogenomic evidence, epidemiological evidence, and documentary evidence all indicate that SARS-CoV-2 entered humans in July-November 2019 (1-2, 83-87, 94-102; therefore arguments based on data for the Huanan Seafood Market on or after mid- to late December 2019--as in Crits-Christoph et al. 2023a,b--cannot, even in principle, shed light on spillover into humans that occurred in July-November, 2019.

When preprints are patently scientifically unsound and have four authors, including a corresponding author, who have committed scientific misconduct on a previous paper on the same subject--as for Crits-Christoph et al. 2023a,b-- there is clear basis to infer the preprints may be product of scientific misconduct, up to and including fraud.

9. Bayesian assessments

Bayesian inference, a method of statistical inference based on Bayes' Theorem, enables calculation of probabilities of hypotheses based on multiple lines of evidence and enables

updating of probabilities of hypotheses as additional lines of evidence become available (120). Bayesian analyses of the origin of COVID-19 have calculated high probabilities for a research-related origin and have calculated increasingly high probabilities for a research-related origin as additional lines of evidence have become available (121-123).

Demaneuf and De Maistre 2020 performed a Bayesian analysis, assessing all evidence on the origin of COVID-19 publicly available as of September 2020--i.e., *before* the release of the NIH grant proposals and progress reports and the DARPA proposal and drafts discussed above in sections 2 and 4--to estimate overall probabilities of an unnatural origin ("lab-related event") or a natural origin ("non-lab-related zoonotic event") (121). Demaneuf and De Maistre 2020 concluded that "under a reference set of input probabilities, the relative probabilities are at least 55% for a lab-related event against 45% at most for a non-lab-related zoonotic event."

Quay 2021 performed a Bayesian analysis, assessing all evidence on the origin of COVID-19 publicly available as of January 2021--i.e., *before* the release of the NIH grant proposals and progress reports and the DARPA proposal and drafts discussed above in sections 2 and 4--to estimate overall probabilities of an unnatural origin ("laboratory origin") or a natural origin ("zoonotic") (122). Quay 2021 concluded that "the probability of a laboratory origin for CoV-2 is 99.8%."

Weissman 2024 performed a comprehensive Bayesian analysis, assessing all evidence on the origin of COVID-19 publicly available as of March 2024--i.e., *after* the release of the NIH grant proposals and progress reports and DARPA proposal and drafts discussed above in sections 2 and 4--to estimate overall probabilities of an unnatural origin ("lab leak," LL) or a natural origin ("zoonotic from wildlife," ZW) (123). Weissman, 2024 concluded that, the odds of an unnatural

origin over a natural origin are extremely high: approximately 66,000 to 1. "Unless one has priors of less than...1/4,400,000, the result favors LL over ZW," and "Combining that likelihood ratio with the point estimate of the prior logit would still give extreme odds, P(LL)/P(ZW) = ~66,000."

10. Formal-risk-analysis assessments

Chen et al. 2024 used the modified Grunow-Finke assessment tool (mGFT), an established risk-analysis tool for differentiating unnatural and natural outbreaks, to study the origin of COVID-19 (124). The mGFT scored 41/60 points (68%), with high inter-rater reliability (100%), indicating a higher likelihood of an unnatural origin than a natural origin.

11. Intelligence assessments

The US Office of Director for National Intelligence writes "The IC continues to investigate how SARS-CoV-2, the virus that causes COVID-19, first infected humans. All agencies assess two hypotheses are plausible: natural exposure to an infected animal and a laboratory-associated incident" (125).

The Federal Bureau of Investigation (FBI), which performs forensic analysis and attribution of biological weapons threats though its National Bioforensic Analysis Center at Fort Detrick MD, assesses with moderate confidence that SARS-CoV-2 entered humans through a laboratory-associated incident (125-127). FBI Director Christopher Wray stated on 02/27/2023 that "The FBI has for quite some time now assessed that the origins of the pandemic are most likely a potential lab incident in Wuhan" (127).

The Department of Energy, which performs forensic analysis and attribution of nuclear, radiological, and biological weapons threats through its Lawrence Livermore National Laboratory "Z Division," assesses with low confidence that SARS-CoV-2 entered humans through a laboratory-associated incident (125-127).

No US intelligence agency assesses with moderate or higher confidence that SARS-CoV-2 entered humans through natural spillover (127).

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Appendix 1: Lapses in US oversight of US-funded gain-of-function research and enhanced potential pandemic pathogens research likely contributed to the origin of COVID-19

The research at the Wuhan Institute of Virology included activities that met the definition of "selected gain of function research" in the US policy in effect in 2014-2017 and that met the definition of "enhanced potential pandemic pathogen research" in the US policy in effect in 2018-present.

Using US funding, provided by the NIH in 2014-2019, the Wuhan Institute of Virology: (1) constructed novel chimeric SARS-related coronaviruses that combined the spike gene of one bat SARS-related coronavirus with the rest of the genetic information of another bat SARS-related coronavirus, (2) showed that resulting viruses efficiently infected human airway cells and efficiently replicated in human airway cells, and (3) showed that the resulting viruses exhibited up to 10,000-fold enhancement of viral growth in lungs, up to 1,000,000-fold enhancement of viral growth in brains, and up to 3-fold enhancement of lethality, in mice engineered to display human receptors on airway cells ("humanized mice").

Although this research met the definition of selected gain-of-function research in the US policy in effect in 2014-2017 (the Pause) and exceeded--by more three orders of magnitude--the threshold set by the NIH for enhancement of viral growth that should trigger immediate cessation of work, and although the NIH was informed of project objectives and results in annual project progress reports in 2016-2018, the NIH failed to flag the project as being covered by the policy, failed to pause the project as required by the policy, and failed to stop the project as required by the Terms and Conditions of the grant.

Although the research also met the definition of enhanced potential pandemic pathogen research in the US policy in effect in 2018-present (the P3CO Framework), and although the NIH was informed of project objectives and results in a proposal for renewal of the grant for 2019-2024, the NIH failed to identify the project as being covered by the policy, and failed to forward the proposal to the HHS P3CO Committee for the risk-benefit assessment required by the policy.

On October 20, 2021, in response to a request from the Ranking Member of the House Oversight Subcommittee, the NIH Acting Director, Lawrence A. Tabak, D.D.S., Ph.D., released a letter on NIH-funded research on bat SARS-related coronaviruses conducted at the Wuhan Institute of Virology and Wuhan University in 2014-2019 (https://www.documentcloud.org/documents/21674679-tabak-letter-to-comer-oct-20-2021). The Tabak letter addressed: (1) NIH funding under grant AI110964, awarded by the NIH to EcoHealth Alliance with subcontracts to the Wuhan Institute of Virology and Wuhan University; (2) the virus WIV1 SHC014 S (mis-rendered as "SHC014 WIV1"), a virus constructed and characterized in Wuhan using NIH funding under NIH grant AI110964;; and (3) the possibility that the virus WIV1 SHC014 S was a proximal progenitor of SARS-CoV-2.

WIV1 SHC014 S is a novel chimeric SARS-related coronavirus that combines the spike gene of one bat SARS-related coronavirus with the rest of the genetic information of another bat SARS-related coronavirus. It is an artificial, laboratory-constructed virus that has no counterpart in viruses that circulate in nature. It is one of at least three artificial, laboratory-constructed chimeric coronaviruses that were constructed by EcoHealth Alliance and its Wuhan partners using NIH funding and that were shown to infect human cells, to replicate in human cells, and to exhibit 10,000- to 1,000,000-fold higher viral growth and higher lethality than the parental natural coronavirus in infection studies in mice engineered to display human receptors

("humanized mice"; https://theintercept.com/document/2021/09/08/understanding-the-risk-of-bat-coronavirus-emergence/; https://republicans-oversight.house.gov/wp-content/uploads/2021/10/Year-5-EHAv.pdf).

The year-4 progress report for the first 5-year term of the NIH grant (submitted to the NIH in March 2018) and the proposal for the second term 5-year term of the NIH grant (submitted to the NIH in November 2018) reported the construction of the three chimeras, the 10,000-fold enhanced viral growth in lungs of humanized mice of the three chimeras, and the enhanced pathogenicity in humanized mice of one of the three chimeras (https://theintercept.com/document/2021/09/08/understanding-the-risk-of-bat-coronavirus-emergence/).

The year-5 proposal for the first 5-year term of the NIH grant (submitted to NIH in August 2021, more than two years overdue, and released to the Ranking Member of the House Oversight Subcommittee together with the Tabak letter) reported that the chimeras exhibited 1,000,000-enhanced viral growth in brains of humanized mice, and exhibited enhanced ability to dasmge lung tissue and 3-fold enhanced lethality in humanized mice (https://republicans-oversight.house.gov/wp-content/uploads/2021/10/Year-5-EHAv.pdf).

The Terms and Conditions of the first 5-year NIH grant stated (https://theintercept.com/document/2021/09/08/understanding-the-risk-of-bat-coronavirus-emergence/):

> Per the letter dated July 7, 2016 to Mr. Aleksei Chmura at EcoHealth Alliance, should any of the MERS-like or SARS-like chimeras generated under this grant show evidence of enhanced virus growth greater than 1 log over the parental backbone strain you must

> stop all experiments with these viruses and provide the NIAID Program Officer and Grants Management Specialist, and Wuhan Institute of Virology Institutional Biosafety Committee with the relevant data and information related to these unanticipated outcomes.

The term "1 log" means "a factor of 10." EcoHealth Alliance and its Wuhan partners created novel chimeras of SARS-related coronaviruses that showed enhanced viral growth by greater than a factor of 10,000...which exceeded, *by three orders of magnitude*, the trigger point for stopping work and reporting results to NIH under the Terms and Conditions of the NIH grant.

The Tabak letter confirms that research reported in the reported in the year-4 and year-5 progress reports of the first 5-year grant and in the renewal proposal for the second 5-year grant--research in Wuhan that generated a potential pandemic pathogen with a greater than 10,000-fold enhanced viral growth, enhanced pathogenicity, and enhanced lethality in humanized mice-- occurred. The Tabak letter thus confirms that NIH funds supported gain-of-function research of concern and construction and characterization of an enhanced potential pandemic pathogen--a pathogen reasonably anticipated, indeed likely, to have enhanced transmissibility and/or pathogenicity in humans--in Wuhan.

The Tabak letter reveals that EcoHealth Alliance and it Wuhan partner failed to report to NIH in a timely manner that they had obtained evidence of enhanced viral growth greater than 1 log over the parental backbone strain. Thus the Tabak letter confirms that EcoHealth Alliance and its Wuhan partner violated the Terms and Conditions of the first 5-year grant,

The Tabak letter also reveals that EcoHealth Alliance failed to submit the year-5 progress report for the first 5-year grant report until more than two years after the submission deadline. Thus the

Tabak letter also confirms that EcoHealth Alliance and its Wuhan partner again violated the Terms and Conditions of the first 5-year grant,

The Tabak letter correctly states that WIV1 SHC014 S and the other novel chimeric SARS-related viruses reported to the NIH by EcoHealth Alliance and its Wuhan partners in their 2018 grant progress report and 2018 grant renewal proposal are insufficiently closely related to SARS-CoV-2 to have served as a proximal progenitor of SARS-CoV-2.

However, the Tabak letter leaves unstated the crucial fact that the NIH has received no information on novel chimeric SARS-related viruses constructed by EcoHealth Alliance and its Wuhan partners subsequent to the 2018 grant progress report and 2018 grant renewal proposal., and therefore that the NIH cannot rule out the possibility that the project created a proximal progenitor of SARS-CoV-2, and cannot even rule out the possibility that the project used NIH funding to create a proximal progenitor of SARS-CoV-2.

The Tabak letter also leaves unanswered the questions of why the NIH, which was provided with relevant data in March of 2018 and again in November of 2018, and which became aware of the failure to submit the year-5 progress report in 2019: (1) failed to act on the violations of the Terms and Conditions of the first 5-year grant, (2) awarded a second 5-year grant period despite the violations of the Terms and Conditions of the first 5-year grant, (3) awarded a second 5-year grant period for a project that proposed continuation of enhanced potential pandemic pathogen research--specifically proposing to construct and characterize additional novel chimeric SARS-related coronaviruses--without forwarding the proposal for HHS-level risk-benefit review as required under the HHS P3CO Framework, and (4) falsely asserted that NIH funding had not supported gain-of-function research or enhanced potential pandemic pathogen research in Wuhan.

Appendix 2: Official, legally controlling, US-government definitions of gain-of-function research and enhanced potential pandemic pathogens research

Policy document: US Government Research Funding Pause on Selected Gain-of-Function Research Involving Influenza, MERS, and SARS Viruses (https://www.phe.gov/s3/dualuse/documents/gain-of-function.pdf).

Policy document: HHS Framework for Research Involving Enhanced Potential Pandemic Pathogens (https://www.phe.gov/s3/dualuse/documents/p3co.pdf).

U.S. Government Gain-of-Function Deliberative Process and Research Funding Pause on Selected Gain-of-Function Research Involving Influenza, MERS, and SARS Viruses

October 17, 2014

U.S. Government Gain-of-Function Deliberative Process and Research Funding Pause on Selected Gain-of-Function Research Involving Influenza, MERS, and SARS Viruses

Gain-of-function studies, or research that improves the ability of a pathogen to cause disease, help define the fundamental nature of human-pathogen interactions, thereby enabling assessment of the pandemic potential of emerging infectious agents, informing public health and preparedness efforts, and furthering medical countermeasure development. Gain-of-function studies may entail biosafety and biosecurity risks; therefore, the risks and benefits of gain-of-function research must be evaluated, both in the context of recent U.S. biosafety incidents and to keep pace with new technological developments, in order to determine which types of studies should go forward and under what conditions.

In light of recent concerns regarding biosafety and biosecurity, effective immediately, the U.S. Government (USG) will pause new USG funding for gain-of-function research on influenza, MERS or SARS viruses, as defined below. This research funding pause will be effective until a robust and broad deliberative process is completed that results in the adoption of a new USG gain-of-function research policy[1]. Restrictions on new funding will apply as follows:

> *New USG funding will not be released for gain-of-function research projects that may be reasonably anticipated to confer attributes to influenza, MERS, or SARS viruses such that the virus would have enhanced pathogenicity and/or transmissibility in mammals via the respiratory route. The research funding pause would not apply to characterization or testing of naturally occurring influenza, MERS, and SARS viruses, unless the tests are reasonably anticipated to increase transmissibility and/or pathogenicity.*

In parallel, we will encourage the currently-funded USG and non-USG funded research community to join in adopting a voluntary pause on research that meets the stated definition.

The deliberative process that will ensue during the period of the research pause will explicitly evaluate the risks and potential benefits of gain-of-function research with potential pandemic pathogens. The presumptive benefits that are generally identified in pursuing this type of research are stated in terms of enhanced ability for earlier awareness of naturally emerging dangerous pandemic pathogens or in the development of medical products in anticipation of such emergence.

However the relative merits of gain-of-function experimental approaches must be compared ultimately to potentially safer approaches. The deliberative process will offer recommendations for risk mitigation, potential courses of action in light of this assessment, and propose methodologies for the objective and rigorous assessment of risks and potential benefits that might be applied to the approval and conduct of individual experiments or classes of experiments. Although the gain-of-function studies that fall within the scope of research subject to the funding pause will be a starting point for deliberations, the suitability of other types of gain-of-function studies will be discussed. It is feasible that the discussion could lead to suggestions of broadening the funding pause to include research with additional pathogens,

[1] An exception from the research pause may be obtained if the head of the USG funding agency determines that the research is urgently necessary to protect the public health or national security.

however, federal Departments and Agencies who fund, support, or perform research should be consulted prior to any additional pathogens being added to the scope of the funding pause.

The deliberative process is envisioned to be time-limited, to involve two distinct, but collaborating, entities, and to be structured to enable robust engagement with the life sciences community. As a first step, the National Science Advisory Board for Biosecurity (NSABB) will be asked to conduct the deliberative process described above and to draft a set of resulting recommendations for gain-of-function research that will be reviewed by the broader life sciences community. The NSABB will serve as the official federal advisory body for providing advice on oversight of this area of dual use research, in keeping with federal rules and regulations.

As a second step, coincident with NSABB recommendations, the National Research Council (NRC) of the National Academies then will be asked to convene a scientific conference focused on the issues associated with gain-of-function research and will include the review and discussion of the NSABB draft recommendations. This NRC conference will provide a mechanism both to engage the life sciences community as well as solicit feedback on optimal approaches to ensure effective federal oversight of gain-of-function research. The life sciences community will be encouraged to provide input through both the NRC and NSABB deliberative processes.

The NSABB, informed by NRC feedback, will deliver recommendations to the Secretary of Health and Human Services, the Director of the National Institutes of Health, and the heads of all federal entities that conduct, support, or have an interest in life sciences research (including the Assistants to the President for Homeland Security and Counterterrorism and for Science and Technology). The final NSABB recommendations and the outcomes of the NRC conference will inform the development and adoption of a new U.S. Government policy governing the funding and conduct of gain-of-function research. Upon adoption of a federal gain-of-function policy, the U.S. Government will declare the end of the research funding pause.

The life sciences community will be informed of progress at regular intervals. The estimated time-line is six months for completion of the two deliberative steps (culminating in delivery of the NSABB recommendations to the HHS Secretary) and three months for the development, approval, and publication of the policy, with the goal of completing the entire process in less than one year from declaration of the research funding pause.

U.S. Department of Health and Human Services

Framework for Guiding Funding Decisions about Proposed Research Involving Enhanced Potential Pandemic Pathogens

2017

Department of Health and Human Services Framework for Guiding Funding Decisions about Proposed Research Involving Enhanced Potential Pandemic Pathogens

Section I. Purpose and Principles

Research involving potential pandemic pathogens (PPPs) is essential to protecting global health and security. However, there are biosafety and biosecurity risks associated with undertaking such research that must be adequately considered and appropriately mitigated in order to help safely realize the potential benefits. The *HHS Framework for Guiding Funding Decisions about Proposed Research Involving Enhanced Potential Pandemic Pathogens* (*HHS P3CO Framework*) is intended to guide HHS funding decisions on individual proposed research that is reasonably anticipated to create, transfer, or use enhanced PPPs. This *HHS P3CO Framework* is responsive to and in accordance with the *Recommended Policy Guidance for Departmental Development of Review Mechanisms for Potential Pandemic Pathogen Care and Oversight* issued by OSTP on January 9, 2017[1] and supersedes the previous *Framework for Guiding Department of Health and Human Services Funding Decisions about Research Proposals with the Potential for Generating Highly Pathogenic Avian Influenza H5N1 Viruses that are Transmissible among Mammals by Respiratory Droplets*[2]. The *HHS P3CO Framework* ensures a multidisciplinary, department-level pre-funding review and evaluation of proposed research meeting the scope outlined herein to help inform funding agency decisions. In so doing, the *HHS P3CO Framework* seeks to preserve the benefits of life sciences research involving enhanced PPPs while minimizing potential biosafety and biosecurity risks.

Section II. Scope and Definitions

For the purposes of this *HHS P3CO Framework*:

A. A ***potential pandemic pathogen*** **(PPP)** is a pathogen that satisfies **both** of the following:

   1. It is likely highly transmissible and likely capable of wide and uncontrollable spread in human populations; and

   2. It is likely highly virulent and likely to cause significant morbidity and/or mortality in humans.

B. An **enhanced PPP** is defined as a PPP resulting from the enhancement of the transmissibility and/or virulence of a pathogen. Enhanced PPPs do not include naturally occurring pathogens that are circulating in or have been recovered from nature, regardless of their pandemic potential.

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[1] Recommended Policy Guidance for Departmental Development of Review Mechanisms for Potential Pandemic Pathogen Care and Oversight. U.S. Government, January 2017.

[2] Framework for Guiding Department of Health and Human Services Funding Decisions about Research Proposals with the Potential for Generating Highly Pathogenic Avian Influenza H5N1 Viruses that are Transmissible among Mammals by Respiratory Droplets. U.S. Government, February 2013.

C. To the extent that transmissibility and/or virulence of PPPs are modified in the following categories of studies, the resulting pathogens are not considered to be enhanced PPPs for the purposes of this Framework[3]:

   1. Surveillance activities, including sampling and sequencing; and

   2. Activities associated with developing and producing vaccines, such as generation of high growth strains.

D. 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 PPPs is subject to additional HHS department-level review as outlined herein.

E. A pathogen previously considered by an agency to be an enhanced PPP should no longer be so considered if the HHS and the White House Office of Science and Technology Policy, in consultation with the Departments of Defense, Homeland Security, Agriculture, and Justice, generally acting through the Federal Bureau of Investigation, jointly determine, on the basis of additional information that has been developed about the risks or the benefits of that pathogen's creation, transfer, or use, that the department-level review processes outlined in this framework are no longer appropriate.

[3] For additional guidance and examples of activities that would and would not be considered to involve enhanced PPP see *Recommendations for the Evaluation and Oversight of Proposed Gain-of-Function Research.* National Science Advisory Board for Biosecurity, May 2016.

Box 1. Criteria for guiding HHS funding decisions on proposed research that involves, or is reasonably anticipated to involve, creation, transfer, or use of enhanced PPPs.

Department-level review of proposed research reasonably anticipated to create, transfer, or use enhanced PPPs will be based on the following criteria:

1) The research has been evaluated by an independent expert review process (whether internal or external) and has been determined to be scientifically sound;
2) The pathogen that is anticipated to be created, transferred, or used by the research must be reasonably judged to be a credible source of a potential future human pandemic;
3) An assessment of the overall potential risks and benefits associated with the research determines that the potential risks as compared to the potential benefits to society are justified;
4) There are no feasible, equally efficacious alternative methods to address the same question in a manner that poses less risk than does the proposed approach;
5) The investigator and the institution where the research would be carried out have the demonstrated capacity and commitment to conduct it safely and securely, and have 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;
6) The research's results are anticipated to be responsibly communicated, in compliance with applicable laws, regulations, and policies, and any terms and conditions of funding, in order to realize their potential benefit;
7) The research will be supported through funding mechanisms that allow for appropriate management of risks and ongoing Federal and institutional oversight of all aspects of the research throughout the course of the research; and
8) The research is ethically justifiable. Non-maleficence, beneficence, justice, respect for persons, scientific freedom, and responsible stewardship are among the ethical values that should be considered by a multidisciplinary review process in making decisions about whether to fund research involving PPPs.

Section III. Review and Oversight Framework

A. The identification, review, and oversight of research subject to department-level review will require responsibilities (Figure 1) of the:

- Funding agency considering funding the proposed research; and
- HHS.

Figure 1: Overview of Responsibilities under the HHS P3CO Framework

Entity	Responsibilities
Funding agency	• Conduct standard scientific merit review; • Refer proposed research that is reasonably anticipated to create, transfer, or use enhanced PPPs for departmental-level review; • Provide relevant information necessary for departmental-level review; • Participate in departmental-level review process, as requested; • Consider the recommendations resulting from the departmental-level review; • Make a funding decision, stipulating terms and conditions of award including additional risk mitigation measures if appropriate; • Report relevant information on funding decisions to HHS and OSTP; • Ensure implementation of and adherence to required risk mitigation procedures and other terms/conditions of award, if funded.
HHS	• Convene a multidisciplinary group to review proposed research that has been determined by the funding agency as being reasonably anticipated to create, transfer, or use enhanced PPPs; • Critically evaluate the proposed research including the risk/benefit assessment and proposed risk mitigation plan; • Consider the eight criteria for guiding HHS funding decisions (Box 1) and additional relevant factors and information; • Develop recommendations on acceptability for HHS funding, including suggestions for additional risk mitigation measures and/or terms and conditions of award, if funded.

B. The HHS department-level review will evaluate proposed research referred by the funding agency that meets the scope outlined in Section II. This review and evaluation will be guided by the criteria listed in Box 1. The evaluation will include consideration of a:

   - Risk/benefit analysis of the proposed research;
   - Risk mitigation plan; and
   - Additional relevant factors.

C. A department-level review will result in recommendations to the funding agency on whether the proposed research is acceptable for HHS funding and what, if any, additional risk mitigation measures should be incorporated into the terms and conditions of award, if funded.

D. If funded, research that is reasonably anticipated to create, transfer, or use an enhanced PPP may require additional risk mitigation strategies which may include, but are not limited to:

   - Modification of the design or conduct of the research;
   - Application of specific or enhanced biosecurity or biosafety and biocontainment measures;

- Evaluation of existing evidence of medical countermeasures (MCM) efficacy, or experiments conducted to determine MCM efficacy against agents or toxins resulting from the research; and
- Methodologies for responsible communication of results.

Section IV. HHS Department-level Review

A. Proposed research that is being considered for funding by the HHS funding agency, is deemed to be scientifically meritorious by an independent internal or external review process, and has been determined by the funding agency to be reasonably anticipated to create, transfer, or use enhanced PPPs must be referred for HHS department-level review.

B. The purpose of the department-level review is to provide a multidisciplinary, pre-funding review and evaluation of proposed research that meets the scope outlined in Section II to recommend whether HHS funding is appropriate, and if so, to help identify the appropriate risk mitigation strategies. The following disciplines should be represented during the department-level review: scientific research, biosafety, biosecurity, MCM development and availability, law, ethics, public health preparedness and response, biodefense, select agent regulations, and public health policy, as well as the funding agency perspectives and other relevant areas. The HHS department-level review group may include non-voting *ex officio* and/or *ad hoc* members from HHS and other federal departments and agencies as deemed appropriate by the Review Group Chair.

C. Extra care in the department-level review should be given to proposed research that is reasonably anticipated to:

- Enhance the harmful consequences of the pathogen;
- Disrupt immunity or the effectiveness of an immunization against the pathogen without clinical or agricultural justification;
- Confer to the pathogen resistance to clinically or agriculturally useful prophylactic or therapeutic interventions against that pathogen or facilitate the pathogen's ability to evade detection methodologies;
- Increase the stability, transmissibility, or the ability to disseminate the pathogen;
- Alter the host range or tropism of the pathogen;
- Enhance the susceptibility of a host population to the pathogen; or
- Generate or reconstitute an eradicated or extinct pathogen.

D. The HHS department-level review may result in the following recommendations:

- Research is acceptable for HHS funding;
- Research is not acceptable for HHS funding;
- Research is acceptable for HHS funding on the condition that certain experiments are modified;

- Research is acceptable for HHS funding on the condition that certain risk mitigation measures are employed at the federal and/or institutional level; or
- Other recommendations, as deemed appropriate.

For research determined to be not in accordance with all of the criteria for guiding HHS funding decisions on proposed research reasonably anticipated to create, transfer, or use enhanced PPPs, a recommendation will be that the research is not acceptable for HHS funding.

Section V. Evaluation of the HHS P3CO Review Process

HHS will periodically re-evaluate and modify this review process, as necessary, to reflect scientific advances and changes to the regulatory landscape. To help inform such evaluations, and to enhance transparency and public engagement in the review and oversight process for enhanced PPP research, HHS will periodically ask the National Science Advisory Board for Biosecurity to review the process described herein.