The Wuhan Laboratory Origin of SARS-CoV-2 and the Validity of the Yan Reports Are Further Proved by the Failure of Two Uninvited "Peer Reviews"

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Opening Statement

A year has passed since the COVID-19 pandemic first started. Its damage so far is astonishing: 127 million people have been infected and, among them, 2.78 million died. These numbers continue to grow at a significant speed, indicating that the pandemic is far from being over. Furthermore, mutant viral strains continue to emerge, and no public policies or treatment strategies seem to be sufficiently effective in blocking COVID-19. There seems to be a consensus that the virus will not be eradicated and humans will continue to live under the influence of COVID-19 in the foreseeable future.

The defeat of humans by COVID-19 is for two fundamental reasons. First, SARS-CoV-2, the causative agent of COVID-19, is not a naturally occurring pathogen but an *Unrestricted Bioweapon*. It has designed and significantly enhanced functions and therefore could not be controlled easily using strategies that would normally work for naturally occurring pathogens. It is a product of the bioweapons program of the Chinese Communist Party (CCP) government, the network of which includes not only the CCP scientists but also certain overseas scientists and organizations. SARS-CoV-2 was created based on template viruses ZC45 and ZXC21, which were originally discovered in bats by scientists of the People's Liberation Army (PLA). The subsequent laboratory modifications had enabled its ability to infect humans as well as had enhanced the virus in its pathogenicity, transmissibility, and lethality.

The second fundamental reason of our defeat was that the world was made to look away from the true nature of SARS-CoV-2 and therefore responded inadequately on multiple aspects and occasions. A massive misinformation campaign has been undertaken by the CCP government to cover up the true origin of SARS-CoV-2, which involved destroying data and samples, publishing fabricated viruses on top scientific journals, controlling the narrative of the origin debate through bribed top scientists and organizations, amplifying the falsified natural origin theory through media control, labeling all other origin theories as "conspiracy theories", and defaming individuals who reveal the truth of SARS-CoV-2. As a result of the CCP's efforts here, the true, weaponized nature of SARS-CoV-2 has been obscured and was not known by most of the public.

One example of the CCP's misinformation campaign is the defamation of the Yan reports.

On September 14th, 2020, we published our first report[1], where we provided abundant scientific evidence and analyses proving that SARS-CoV-2 must not be a product of natural evolution but a product of laboratory creation. We also postulated/reconstructed, based on substantial literature evidence, a pathway for the convenient laboratory creation of SARS-CoV-2. On October 8th, 2020, we published our second report[2], where we used scientific evidence and logical analyses to uncover a large-scale, organized scientific fraud committed by the CCP laboratories and orchestrated by the CCP government. This fraud clearly indicates that SARS-CoV-2 is not a natural occurring virus or a simple gain-of-function product that accidentally leaked out from a laboratory. Rather, it must be a deceiving, non-traditional bioweapon created by the CCP regime. We also refuted the claim that the virus was derived from a virus from a mine in Mojiang. Furthermore, the fact that certain fabrications preceded the initial outbreak of COVID-19 suggests that the release of the SARS-CoV-2 must be intentional.

Our two reports were published on *zenodo.org* as preprint articles. We chose this site and this format because we were fully aware of the censorship on the laboratory origin of SARS-CoV-2 imposed by the top scientists of the field – peer review would not allow our report to be published as it is in a timely manner or at all. The transparency and expedited publication process offered by *zenodo*, however, were necessary and appropriate in this situation – Dr. Yan and the rest of us wanted the truth of SARS-CoV-2 to be known by the rest of the world as early as possible. Furthermore, peer review is not a guarantee for scientific quality or truthfulness[3-7], which is a view shared by many experts, including Dr. Anthony Fauci.

After the publication of our first report, within ten days, two uninvited "peer reviews" were published[8,9]. As shown in the rest of the document, these reviews were completely mistaken and intentionally misleading. However, they were published on well-known platforms and were produced by "reviewers" who hold high academic titles and are affiliated with prestigious institutions. It was a fine display of the status of personnel and organizations engaged in the CCP's scientific misinformation.

However, before diving into details of these "peer reviews", let us travel back in time and take a quick tour to review Dr. Yan's journey since the beginning of the COVID-19 pandemic as well as some early events in the origin "debate".

A brief timeline

On December 31st, 2019, Dr. Yan, a virologist and a then core team member of *the WHO H5 Reference Laboratory* and *the State Key Laboratory of Emerging Infectious Diseases of China* at the University of Hong Kong School of Public Health, conducted a secret investigation on the outbreak in Wuhan. On Jan 16th, 2020, Dr. Yan conducted a second investigation. On both occasions, Dr. Yan used her personal connections inside China's research and hospital systems, including PLA laboratories and hospitals, and the CDC. Through communications with them, Dr. Yan learned first-hand information of the emerging COVID-19 disease, including its severity and scale of spread. She also learned how the CCP government was hiding such information from the public, which was deeply worsening the situation. Dr. Yan then gave timely feedback to her supervisors, professors Leo LM Poon and Malik Peiris, who are top coronavirus experts and core consultants of the WHO. She had hoped that certain actions would be taken internationally to pressure the CCP government to act responsibly. However, no such actions took place. Instead, Dr. Yan was warned repeatedly by professor Poon that she "*should not cross the red line*" and, "*if not, would be disappeared*".

At the same time, Dr. Yan also obtained intelligence information about the true identity of the SARS-CoV-2 virus – a bioweapon created by the Chinese military. She then verified this herself by analyzing the genetic information of the virus shared on the database using her own expertise in virology and biology. While chasing the initial sequence information, Dr. Yan also noticed that strange changes were made to the earliest deposited SARS-CoV-2 sequence. The first version of the genomic sequence, which was uploaded on January 12th was strangely mistaken. It was then quickly withdrawn and replaced by the

second version (MN908947.2) on Jan 14th, which was largely correct. It is noteworthy that, on January 13th, Thailand reported the first case of infection outside China, which entails that sequence information would be obtained by the outside world and no longer under the full control of the CCP government. What is also noteworthy is that the first version was not accessible on the database for a long while until it reappeared (MN908947.1), surprisingly, free of the severe errors that it had carried previously. Finally, on January 17th, a third version was uploaded and some missing nucleotides were added to the sequence (MN908947.3). The intelligence information, the genetic evidence, the severity of the disease, and the cover-up by the CCP government convinced Dr. Yan that a public health crisis may be forthcoming.

This great sense of urgency compelled Dr. Yan to seek alternative avenues to let this information go out to the public. Her hope was, once again, to alert the world and trigger certain international pressure to make the CCP government act responsibly, which may then prevent a global health crisis. On Jan 19th, 2020, she anonymously shared this information on the *LUDE Media*, a YouTube channel that broadcasts to a great Chinese audience both inside and outside mainland China. In this broadcast[10], Dr. Yan sent the following five messages:

- The virus was created in a PLA laboratory using ZC45/ZXC21 as the template.
- The CCP government is actively covering up the true information of the disease.
- There is human-to-human transmission.
- There are no wild animal intermediate hosts, and the Huanan seafood market is not the origin of the virus.
- If not controlled immediately, the virus may lead to a pandemic and, as a result, many mutants will emerge inevitably and rapidly.

The red line had been crossed. Dr. Yan knew very well then that her actions could lead to severe consequences in her personal safety. If her identity was revealed, she could be "disappeared", just like what happened to thousands of Hong Kong youths during the pro-democracy protests since June 2019. Dr. Yan did it anyways.

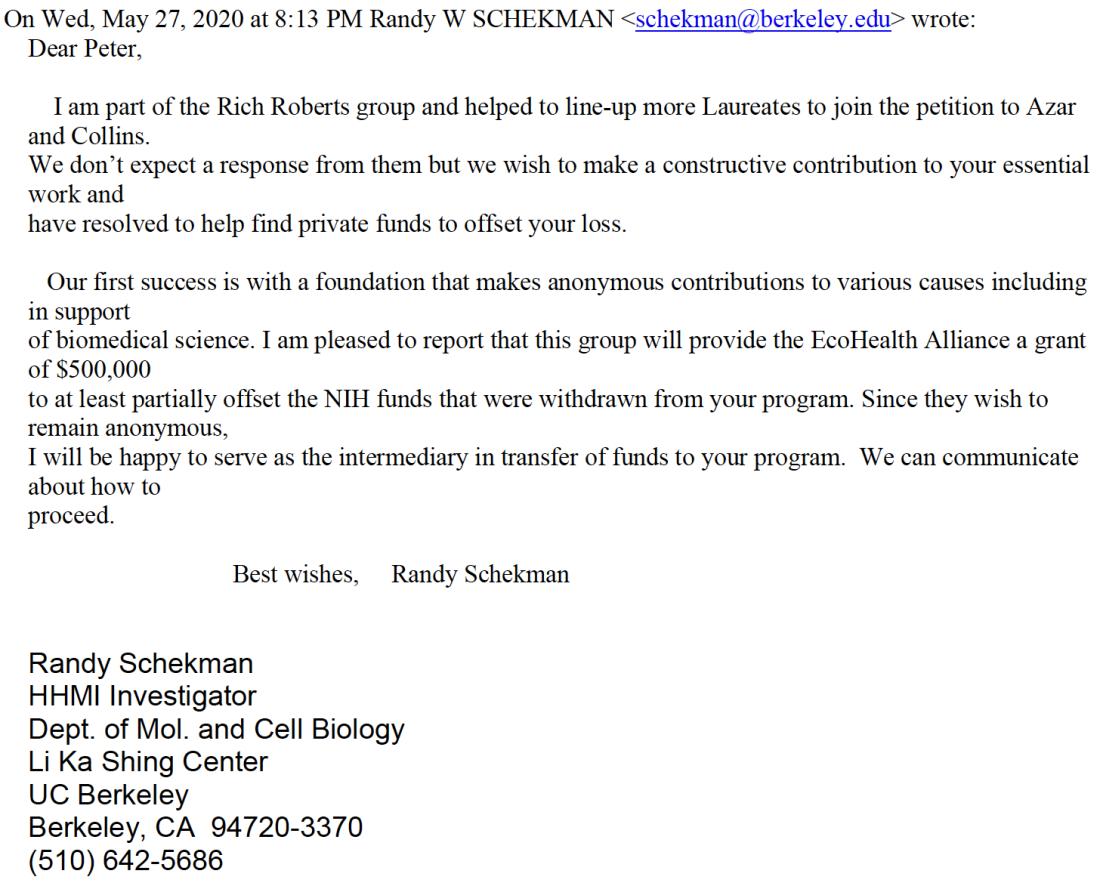
The effect of Dr. Yan messages was immediate and significant. The CCP government was shocked by the substantial truth in Dr. Yan's messages; it was afraid that this anonymous insider was going to expose more of its lies. With its original plans disrupted, the CCP government reacted in a hurry:

- Four hours after *LUDE Media*'s broadcast, the CCP government tripled their official number of infections, increasing it from 62 to 198.
- A few hours later, the CCP government reported, for the first time, infections outside of Wuhan.
- It also made a nation-wide announcement elevating the infectious disease alertness to the highest level according to the *Law of the People's Republic of China on the Prevention and Treatment of Infectious Diseases*.
- Within one day, the CCP government admitted for the first time that there was human-to-human transmission.
- Three days later, Wuhan was put into lockdown.

At the same time, the scientific field has been mobilized. In China, Dr. Zhengli Shi, the *batwoman* from the Wuhan Institutes of Virology (WIV), hurried out a *Nature* publication (submitted on January 20th and published on February 3rd, 2020)[11], where she reported a RaTG13 bat coronavirus sharing a 96.2% sequence identity with SARS-CoV-2. Since then, this RaTG13 virus has served as the founding evidence for the natural origin theory (this publication of Shi has been accessed over 1.11 million times and cited 5431 times by March 30th, 2021). Interestingly, in the same issue of *Nature*, a similar article was published by Dr. Yongzhen Zhang[12], which described ZC45 and ZXC21 as the closest match to SARS-CoV-2 evolutionarily. However, Dr. Zhang's publication received much less attention (0.47 million accesses and

2588 citations by March 30th, 2021). On February 8th, 2020, Major General and bioweapon expert Dr. Wei Chen took over the leadership of the WIV. Furthermore, a compulsory regulation was put into place demanding that all manuscripts concerning SARS-CoV-2 research produced by Chinese laboratories must be first reviewed and approved by the CCP government before being submitted for publication.

Significant movements had also taken place in the scientific circle in the west. On February 19th, 2020, a statement signed by 27 experts was published on the influential journal *Lancet*[13]. In this statement, the scientists asserted a natural origin of SARS-CoV-2 and condemned "conspiracy theories" that suggested a laboratory origin of the virus. It was later revealed through exposed email exchanges that, intriguingly, their assertion on the virus' origin was accepted by the signees in the absence of any scientific discussions or supporting evidence[14,15]. Furthermore, the statement was organized secretly by Dr. Peter Daszak, CEO of the non-profit *EcoHealth Alliance* and long-term collaborator of Dr. Zhengli Shi and the WIV. In fact, it was through Daszak and *EcoHealth Alliance* that millions of NIH funding, which are US tax dollars, were channeled to the WIV and used presumably in military-civil fusion projects there. This conflict of interest (COI) was very likely what prompted Daszak to keep his central role in the *Lancet* statement under the radar. Though, the same COI somehow failed to discourage him from leading the WHO investigation of the origin of COVID-19 in 2021 and subsequently "concluding" that SARS-CoV-2 is "*extremely unlikely*" to have come from a laboratory. Interestingly, when the NIH funding was discontinued for *EcoHealth Alliance* in 2020, Daszak was immediately offered a donation of half a million dollars from an anonymous foundation (Figure 1). It is not known whether or not this donation played any role in encouraging Daszak's actions in supporting the CCP government.



On Wed, May 27, 2020 at 8:13 PM Randy W SCHEKMAN <schekman@berkeley.edu> wrote:

Dear Peter,

I am part of the Rich Roberts group and helped to line-up more Laureates to join the petition to Azar and Collins.
We don't expect a response from them but we wish to make a constructive contribution to your essential work and
have resolved to help find private funds to offset your loss.

Our first success is with a foundation that makes anonymous contributions to various causes including in support
of biomedical science. I am pleased to report that this group will provide the EcoHealth Alliance a grant of $500,000
to at least partially offset the NIH funds that were withdrawn from your program. Since they wish to remain anonymous,
I will be happy to serve as the intermediary in transfer of funds to your program. We can communicate about how to
proceed.

Best wishes, Randy Schekman

Randy Schekman
HHMI Investigator
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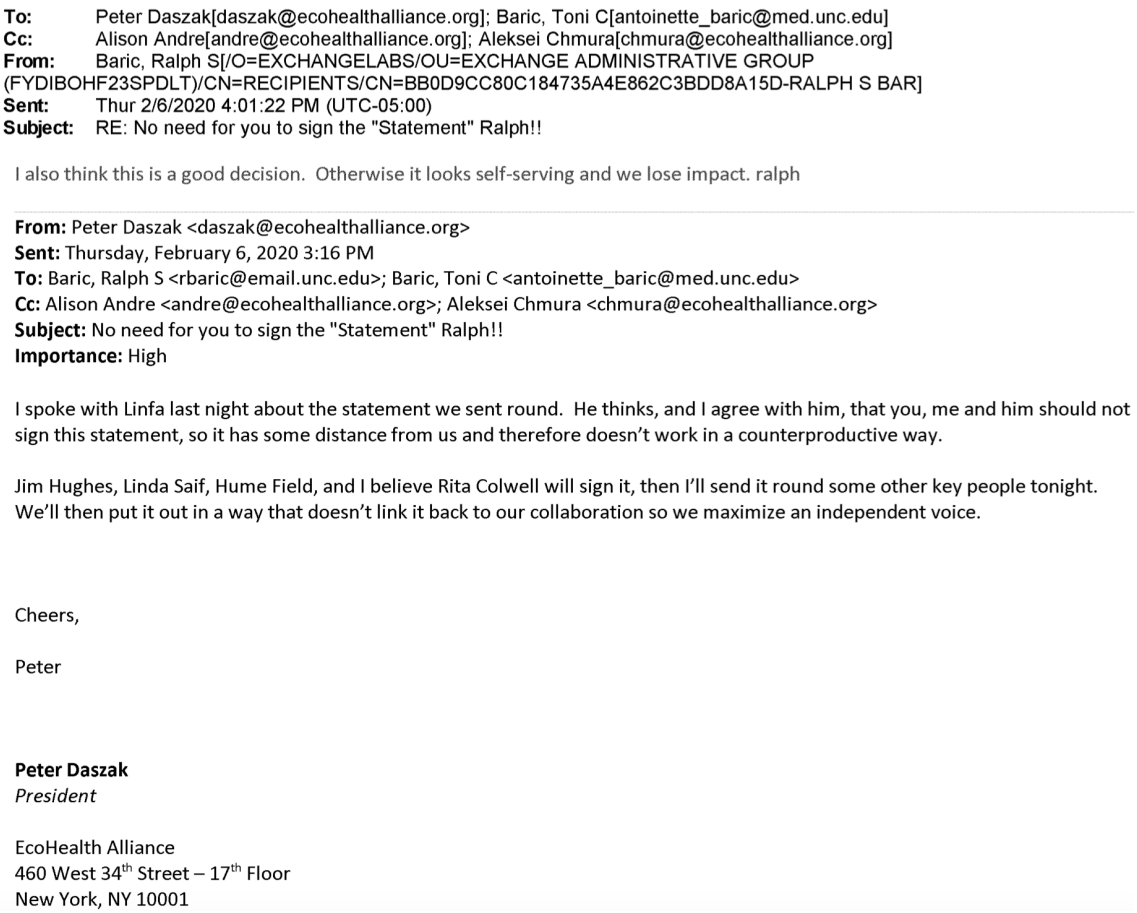
Figure 1. Exposed email shows that an anonymous donation of $500,000 was made to EcoHealth Alliance to partially offset the NIH funds withdrawn.

It is also worth mentioning that Dr. Linfa Wang from Duke-NUS Medical School and Dr. Ralph Baric from the University of North Carolina, both long-term collaborators of Zhengli Shi and the WIV, also consciously distanced themselves from the *Lancet* statement to make sure that the statement "*doesn't link back to our collaboration*" because "*(o)therwise it looks self-serving and we lose impact*" (Figure 2)[16].



To: Peter Daszak[daszak@ecohealthalliance.org]; Baric, Toni C[antoinette_baric@med.unc.edu]
Cc: Alison Andre[andre@ecohealthalliance.org]; Aleksei Chmura[chmura@ecohealthalliance.org]
From: Baric, Ralph S[/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=BB0D9CC80C184735A4E862C3BDD8A15D-RALPH S BAR]
Sent: Thur 2/6/2020 4:01:22 PM (UTC-05:00)
Subject: RE: No need for you to sign the "Statement" Ralph!!

I also think this is a good decision. Otherwise it looks self-serving and we lose impact. ralph

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From: Peter Daszak <daszak@ecohealthalliance.org>
Sent: Thursday, February 6, 2020 3:16 PM
To: Baric, Ralph S <rbaric@email.unc.edu>; Baric, Toni C <antoinette_baric@med.unc.edu>
Cc: Alison Andre <andre@ecohealthalliance.org>; Aleksei Chmura <chmura@ecohealthalliance.org>
Subject: No need for you to sign the "Statement" Ralph!!
Importance: High

I spoke with Linfa last night about the statement we sent round. He thinks, and I agree with him, that you, me and him should not sign this statement, so it has some distance from us and therefore doesn't work in a counterproductive way.

Jim Hughes, Linda Saif, Hume Field, and I believe Rita Colwell will sign it, then I'll send it round some other key people tonight. We'll then put it out in a way that doesn't link it back to our collaboration so we maximize an independent voice.

Cheers,

Peter

Peter Daszak
President

EcoHealth Alliance
460 West 34th Street – 17th Floor
New York, NY 10001

Figure 2. Exposed email shows Peter Daszak, Linfa Wang, and Ralph Baric purposely avoided signing the Lancet statement although Daszak eventually signed likely because of the central role he played in organizing this statement.

In addition to the *Lancet* statement, on March 17th, 2020, an opinion article titled "*The Proximal Origin of SARS-CoV-2*" was published on the top journal *Nature Medicine*[17]. Here the authors also asserted a natural origin of SARS-CoV-2 despite that no convincing evidence was provided and that their theory was built upon the fabricated RaTG13 virus published by Zhengli Shi. Among the five authors of this article was Dr. Ian Lipkin from Columbia University, who, like Daszak, has close ties with China and has received several prestigious awards from the Chinese Communist Party (CCP) government in the past two decades[18,19].

The *Lancet* statement and the *Nature Medicine* article, although baseless scientifically, both concluded that SARS-CoV-2 is a natural occurring pathogen. These publications had subsequently been promoted greatly on traditional media, social media, and other platforms. The result of these combined operations was to declare to the scientific community: *SARS-CoV-2 having a natural origin is the official, accepted view; any dissenting voices would be condemned and dismissed by experts of the field*.

Therefore, unsurprisingly, although various scientific evidence continued to emerge pointing to the laboratory origin of SARS-CoV-2, much of such information was suppressed fairly efficiently. The public's opinion of the virus' origin remained dominated by the natural origin theory.

However, the truth was not meant to be blocked. While Dr. Yan continued to use the *LUDE Media* to expose various facts of COVID-19, including providing intelligence information (For example, pointing out that the *Lancet* statement was an organized effort to suppress the laboratory origin theories) and sharing her expert analyses on aspects of asymptomatic infections, antibody evaluation, autopsy studies, treatment strategies, vaccine development, etc., her identity was eventually discovered by the CCP government, which forced her to leave Hong Kong. At the end of April 2020, Dr. Yan successfully escaped from Hong Kong and arrived at the US. Here she continued to reveal the truth of SARS-CoV-2 to the world. On July 10th, 2020, Dr. Yan made her first public appearance on *Fox News* and, since then, has been continuing to spread the truth of COVID-19 on different platforms. The CCP's defamation of Dr. Yan, which took place on both traditional media and social media involving CCP's cyber army, also started right after Dr. Yan's escape and came in huge waves continuously since then.

Uninvited "peer reviews" on our report were extremely poor scientifically and meant to mislead

On Sep 14th, 2020, Dr. Yan and the rest of us authors published our first scientific report[1], presenting substantial scientific evidence and analyses to prove that SARS-CoV-2 is a product of laboratory creation. Since then, the origin of SARS-CoV-2 has become an open secret to people who have the relevant knowledge and have carefully analyzed our report, although some of these honest opinions may not have been made public for various reasons. The report has gained its fair share of attention so far, reaching over 1.1 million views and over 0.75 million downloads.

Interestingly, almost immediately after its publication, our report received "peer reviews", although uninvited, from two groups of scientists, respectively. The first review, published on September 22nd, 2020, eight days from the publication of our report, was produced by a group of four scientists from the *Johns Hopkins Center for Health and Security*: Kelsey Warmbrod, Rachel West, Nancy Connell, and Gigi Gronvall[8]. Two days later, on September 24th, a second review was published by the *MIT Press*, where comments came from four seemingly independent scientists: Takahiko Koyama, Adam Lauring, Robert Gallo, and Marvin Reitz[9].

It has to be mentioned that no "reviews" came from the coronavirus research community. The WIV and the Academy of Military Medical Sciences (AMMS) also kept silent despite that the scientific evidence provided in our reports clearly and repeatedly pointed to them as the responsible parties for the creation of SARS-CoV-2.

Although we welcome critical reviews of our report, such reviews have to be evidence-based, logical, honest, unbiased, and produced by qualified scientists. Unfortunately, these two published "reviews" did not meet any of those criteria.

The four "reviewers" at the *MIT Press* showed severe misunderstanding and lack of knowledge in coronavirus biology. They practically ignored the large body of evidence and analyses in our report and, through this practice, unfairly described our report as "lack of evidence". On the other hand, their own judgements were based on a series of published "scientific findings", which have been now proven to be fraudulent. Therefore, their review comments, which are exclusively criticisms of our report, are of no scientific strength at all.

These "reviewers" at the *MIT Press* also violated the rules of peer review. Dr. Robert Gallo and Dr. Marvin Reitz published practically identical comments on multiple occasions, which indicates clearly that at least one of the two has committed plagiarism and that their review comments were not all results of independent, critical thinking.

Furthermore, the "reviewers" at the *MIT Press* politicized the issue when their job as "peer reviewers" was to judge the science of our scientific report in an unbiased manner. ~~They questioned our affiliation to~~

~~the *Rule of Law Foundation* and *Rule of Law Society*. Our choosing of these two organizations as our affiliation was because we appreciate their crucial assistance in Dr. Li-Meng Yan's escape from Hong Kong. The twin organizations are non-profit organizations that work to promote freedom, human rights, and equality for Chinese people. They have financed Dr. Yan's flight from Hong Kong and provided a stipend for her to get settled in the US. Without this help, Dr. Yan would not have the chance to tell the truth of COVID-19 to the world and much evidence within the Yan reports may not be revealed in a timely manner.~~ However, importantly, the science in the Yan reports was produced solely by us scientists and has not been altered in any way by the two foundations or their founders.

(*Comments on July 17th, 2021*: Because the ROLF & ROLS unilaterally requested to have our reports closed, which violated the rules of scientific publications, we have changed our affiliation in responding to this situation. Relevant contents in the above paragraph were crossed out because we believe our earlier views on this matter were misled and such descriptions do not truthfully reflect real events.)

The "reviewers" at the *MIT Press* also questioned the timing of the publication of the first Yan report. However, the publication of our report was not the only thing that Dr. Yan did to alert the world about the public health threat of COVID-19 or the artificial nature of the SARS-CoV-2 virus. Dr. Yan first revealed these truths on January 19th, 2020. She cautioned the world then that a global pandemic would be unavoidable if her revelation about the artificial, weaponized nature of the virus was not taken seriously. Since then, through the *LUDE Media*, Dr. Yan continued to reveal various facts of COVID-19. After escaping from Hong Kong, Dr. Yan also went onto different platforms, for example, *Fox News* and *Daily Mail*, to continue to alert the world. The publication of the first Yan report was only one of those efforts. More importantly, like with any other manuscript, the preparation of the first Yan report, which took a significant amount of time and efforts of the authors, followed its natural course until it reached publication quality in September 2020.

Interestingly, while criticizing the timing of our report, this MIT Press review itself was published in a hasty manner – only ten days after the publication of our report. In their comments, they also expressed, repeatedly, their doubts on our statement that we have a second report to publish. In fact, the second Yan report was published on October 8th, 2020[2], only 15 days after the appearance of the *MIT Press* "review". Apparently, it was these reviewers, not us, who felt some urgency in terms of timing.

There seems to be an intriguing question here: *while the timing of Dr. Yan's actions has always been consistent with her commitment to global health and revealing the truth of COVID-19, what is behind the urgency or timing of the MIT Press in publishing the review to negate the Yan report?*

The uninvited "peer review" published by the *Johns Hopkins* researchers are even poorer in terms of scientific vigor. These four scientists, Warmbrod, West, Connell, Gronvall, showed a complete lack of understanding in every branch of biology that was relevant to the topic. Some of their comments were plainly ignorant, which makes responding to them feel like grading exams of clueless students – they were piling up key words to get partial credits and at the same time have no idea what they are talking about.

What was even more ridiculous with Warmbrod et al.'s "review" was that, in almost every comment, these four "reviewers" intentionally distorted the original descriptions in our report. By doing so, they then invented room, which did not exist otherwise, to insert criticisms. Their actions have then falsified a scene: our report was full of mistakes and the "reviewers" themselves appeared to be superior scientists that hold the truth. The reality, however, is that they had only rudimentary understanding of the science here. Yet, they abused their tiny advantage over the public on this knowledge as well as their academic brand to fool the public and to defame our report.

When the quality of these two sets of uninvited "peer reviews" is so poor, one has to wonder why these "reviewers" would rush out their shoddy judgements publicly? Did they not realize that this is a

global health issue and that the world would suffer from misinformation coming from irresponsible, unqualified scientists?

There may be some clues to this mystery.

Dr. Robert Gallo, the leading "reviewer" at the *MIT Press*, has deep ties to the CCP government. In 2009, the *Gallo Virology Institute* was established in Shandong Province, China[20]. Gallo is also a member of the management team for the Hong Kong-based company, *Medisun Holdings Limited*[21]. Furthermore, interestingly, on December 20th, 2020, three months after Dr. Gallo published his review criticizing our report, the CCP government gave him the *VCANBIO Award for Biosciences and Medicine*, one of the most prestigious awards in China[22]. Enormous praises were placed on Gallo when this news was reported across many media platforms. These connections and the long-term "friendship" that Gallo has with the CCP government leave little doubt on why Dr. Gallo would come out and baselessly criticize the Yan report – he should have been encouraged or even directed by the CCP government.

Based on her interview at *CNNpolitics* published on October 21st, 2020, Dr. Gigi Gronvall appears to be the leading figure of *the Johns Hopkins* "reviewers". As revealed recently[23], Gronvall was a member of the expert group, who was consulted by the US government very early on in the pandemic about the origin of SARS-CoV-2. The now-exposed email exchanges show that Gronvall and other scientists (including Peter Daszak, Kristian Andersen, Trevor Bedford, Stanley Perlman, etc) in this group formed an agreement that the virus must have come from nature despite that there is an absence of supporting evidence. Interestingly, Gronvall's actions then and her review of our report later have been consistent – she came to this conclusion in the absence of supporting evidence or analyses. Whether her past stance urged her to publish the biased, baseless review and thus muddle the water on the origin of SARS-CoV-2 is everyone's guess.

It is necessary to point out that, comparing to the enormous "scientific criticisms" that our first report has received, not a single "review" or any scientific counter-argument was made toward our second report. The same trend was seen in the media world: while news articles thrashed our first report, no news article, to the best of our knowledge, was published specifically attacking our second report. It is intriguing that whatever incentives encouraged the two uninvited "peer reviews" against our first report did not succeed in motivating anyone to "review" our second report. Given that such incentives tend to be huge, the absence of "peer review" here can be seen as a proof that our second report is even more unbeatable scientifically.

Although the two "reviews" on our first report were so poor in quality that any scientist with the proper knowledge would automatically disregard them, they did spread widely through the media. *National Geographics*, *New York Times*, and *CNN*, all cited these reviews, without any fact check, to criticize Dr. Yan and our report. As described previously in our response to *CNN*[24], although *CNN* offered to interview Dr. Yan, it did not accommodate Dr. Yan's request that she would only do live interviews with *CNN*. The CCP government also put a spin on these news articles published in the western media to further defame Dr. Yan and thereby further suppress the truth of the SARS-CoV-2 origin.

This round of scientific misinformation and media manipulation, once again, caused great confusion in the general public. We therefore felt that responses from us would be beneficial as they may help the world defeat such misinformation and arrive sooner at the truth of COVID-19. So, as we have promised in our second report, here we present our point-to-point responses to the review comments from both groups of "reviewers".

This document has an excessive length in part because we often had to cite the exact words from our report to prove that the "reviewers" intentionally distorted our original descriptions. On the positive side though, on a few occasions, we did use room to further clarify certain points, which should benefit people

outside the coronavirus research circle as they may not have fully appreciated certain evidence from reading our report. These issues include but are not limited to:

- Why ZC45 and ZXC21 must have been used as the template for the creation of SARS-CoV-2.
- How ~3,000 nucleotide changes (~10% of the viral genome) could be safely introduced to the template.
- Why these changes are necessary in concealing the bioweapon-nature of SARS-CoV-2.
- Whether or not these changes could bear additional designed functions, which may be associated with unique pathogenic outcomes.
- How Zhengli Shi and her important collaborators (Lanying Du, Shibo Jiang, Ralph Baric, Fang Li, etc.) learned early on the two most essential elements in Spike engineering for human infection: receptor binding and presence of human protease-cleavage site[25]. (*It is also worth mentioning that, Yusen Zhou, husband of Lanying Du and an AMMS expert in the understanding of immune evasion strategies of coronaviruses, suddenly passed away in summer 2020. Right before his passing, on April 29th, 2020, a manuscript was submitted by his research group to Science[26]. This work described the Spike N501Y mutation, which was later shown to be the determining mutation of the prevalent UK variant B.1.1.7. that emerged in the human population a few months afterwards in the fall.*)

Structurally, our point-to-point responses here are separated into two parts. *Part I* are our responses to the "review" published by the *MIT Press* and *Part II* are responses to the "review" published by the *Johns Hopkins* "reviewers". In both parts, our responses are colored in black, while the original "review" comments are in blue. At the end of each part, our references are provided, also in black. Please note that references in different parts partially overlap with each other as we have intended to make each part a separate, stand-alone piece of writing.

Significance in acknowledging SARS-CoV-2 as an *Unrestricted Bioweapon*

As shown in the remainder of the document, our responses here further prove that the science in our reports is solid and irrefutable. We urge the public and relevant governments to face the truth revealed in our reports: SARS-CoV-2 is an *Unrestricted Bioweapon* created by the CCP regime.

A

B

图书在版编目(CIP)数据

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C

4. 使用目的已超越军事 和传统基因武器相比,在未发生世界大战之情况下,使用当代基因武器之目的主要不是军事企图,而是重要的恐怖威胁、政治和地区或国际战略之需求。虽然,战争或军事动作是完成政治任务之重要或最后选项;但其明目张胆,暴露于光天化日之下,易受别国和世人之谴责。若采用当代基因武器,则隐蔽,难于取证;即使提供学术证据甚至病毒和动物等实证,亦可百般抵赖,阻止和压制,使国际组织和正义人士无可奈何。

4. Usage beyond military. Unlike traditional genetic weapon, in the absence of a world war, the main goal of using contemporary genetic weapon is not for military purposes, but for causing terror (in) and gaining political and strategic advantage, regionally or internationally, (over the enemy state). Although warfare or military actions remain an important and often the last option in reaching a political goal, they are too obvious, exposed completely under the sun, and therefore prone to be condemned by other countries and the international community. In the case of contemporary genetic weapon, its usage is deceiving and hard to prove. Even if scientific, virological, and/or animal evidence were in place (to support the accusation), (one can) deny, prevent, and suppress (the accusation of bioweapon usage), rendering international organizations and the justice side helpless and unable (to make the conviction).

Figure 3. The 2015 book "Unnatural Origin of SARS and Genetic Weapons Based on Artificial Human-Infectious Viruses". A) Chief editors: Dezhong Xu (Major General of PLA, leading PLA epidemiologist & SARS expert) and Feng Li (Vice Director, Health Bureau of the PLA General Logistics Department). B) Publication details. Publisher: Military Medical Science Press. C) Description of some key features of contemporary genetic weapon in Chinese (top, Chapter 4, Page 85) and its translation in English (bottom).

The concept of *Unrestricted Bioweapon* may be new to the rest of world, but to the CCP it is not. Such a novel bioweapon had been developed by the CCP secretly for a long while, and the term "*Unrestricted Bioweapon*", which was first coined by us in the second Yan report, describes this novel bioweapon perfectly. In fact, the CCP did not hide its intention here. In a book published in 2015 (Figure 3), a group of CCP's military virologists/scientists headed by professor and Major General Dezhong Xu described an ideal "*contemporary genetic weapon*". The key features of it include:

- It would be created in a way that it is practically indistinguishable from a naturally occurring pathogen. This way, "*even if scientific, virological, and/or animal evidence were in place (to support the accusation), (one can) deny, prevent, and suppress the accusation of bioweapon usage, rendering international organizations and the justice side helpless and unable to make the conviction*".
- Its use is not restricted for military battles, but is for non-military settings where it would be "*causing terror (in) and gaining political and strategic advantage, regionally or internationally, (over the enemy state)*".

Combining the above descriptions with professor Ralph Baric's assessment that "*you can engineer a virus without leaving any trace*"[27], people may finally be able to connect the dots and peel off the many layers to access the core of the COVID-19 pandemic.

(*A future report from us will focus on further describing Unrestricted Bioweapons as well as proposing actions in facing the attack by such a weapon*)

As revealed in our second report, the scientific misinformation and cover-up by the CCP started before the initial outbreak, which indicates that the release of the SARS-CoV-2/bioweapon was not accidental but should be intentional. Evidence suggests that the outbreak should have originated from community tests of the bioweapon that went out of control. As Dr. Yan shared through the *LUDE Media* on January 19th, 2020[10], community testing is a key step of the CCP's unrestricted bioweapons plan. The goal of community testing could include: 1) To observe the bioweapon's effect on its intended target – humans; 2) To further adapt the virus in humans and the environment and thereby give the virus a more natural look. However, due to the lack of proper animal models, the CCP scientists should have underestimated the transmissibility of SARS-CoV-2 and, as a result, the containment strategy used in the community tests somehow failed, leading to the release of this bioweapon. In a way, intentional release here refers to the conscious actions of the CCP scientists during the community tests – they took the virus out of the P3/P4 laboratory and released it in the community as part of its development. After the virus got out of hand, however, the CCP government did not really control it. Instead, it took advantage of the outbreak and made sure that the virus spread to and hurt other parts of the world by doing at least the following:

- It stopped domestic travel and yet allowed international travel from Wuhan.
- It hoarded the PPE and thereby greatly worsened the COVID-19 crisis in other countries.

Because of the CCP's long-term planning, which includes pre-installing scientific fabrications[28,29] and pre-establishing relationships with certain western experts, organizations, journals, and media, the *Unrestricted Biowarfare* then took off conveniently around the globe and yet was sufficiently covered up.

It is also important to realize that a bioweapon could carry designed and added functions, which naturally occurring pathogens of the same kind may not have. This level of awareness should be the key in finding answers to the many unknowns of the COVID-19 disease. It needs to be investigated whether any of the following symptoms and/or phenomena, which are concerning and somewhat mysterious, be results of artificial design:

- *Coagulopathy:* Distinct from other viral illnesses, coagulopathy is frequently observed in COVID-19 patients and is often life-threatening with poor prognosis[30-33]. COVID-19-associated coagulopathy may occur in a wide range of organs, taking the forms of arterial and venous thromboembolism or systemic microangiopathy[34-38].
- *Neurological damage*: Many COVID-19 patients also experience neurological damage[39-42], the reason for which is not known and has to be studied carefully. Interestingly, the template viruses ZC45 and ZXC21, upon their discovery, were shown by the PLA scientists to cause brain infections and inflammation in suckling rats[43]. Coincidentally or not, the E protein, which is associated to neurotoxicity in coronavirus infections[44], was kept 100% identical between ZC45/ZXC21 and SARS-CoV-2.
- *Autoimmune disorders*: Overactive immune response contribute significantly to the pathogenesis of COVID-19[35,36,45,46]. Autoimmune disorders secondary to SARS-CoV-2 infections present similar clinical manifestations as systemic autoimmune diseases and may result in damages in a wide range of organs in many age groups. COVID-19-induced autoimmune disorders include systemic lupus erythematosus (SLE)-like syndrome[47-49], kawasaki-like syndrome[50-53], and immune thrombocytopenic purpura (ITP)[54-56].
- *Long hauler*: A significant percentage of infected individuals become long haulers. They develop various complications in multiple systems[57-60], which adversely affect the quality of their lives and are very difficult to treat. Diagnosis for long haulers is also difficult. The medical reasons behind and molecular basis of long haulers need to be investigated thoroughly.
- *Antibody-Dependent Enhancement (ADE)*: ADE refers to the general situation where certain antibodies generated from the infection of one viral variant may lead to harmful effects during reinfection by a different variant of the virus. ADE is a confirmed phenomenon in SARS, Dengue, and other viral infections. Studies have shown that ADE may exacerbate SARS-CoV-2 infections[61-64]. While mutant variants of SARS-CoV-2 continue to emerge, understanding ADE may be critical in the treatment and prevention of SARS-CoV-2 infections as well as the development of safe vaccines[65].

In addition to realizing SARS-CoV-2 as an *Unrestricted Bioweapon*, people should also come to the realization that the CCP's *Unrestricted Scientific Misinformation* campaign is a significant component of this *Unrestricted Biowarfare*. Many people and organizations were put into work by the CCP and functioned in a highly coordinated manner, including scientific experts (CCP scientists and experts from other countries), scientific journals (*Nature*, *Lancet*, etc), research institutions (WIV, AMMS, etc), and international organizations such as the WHO. The *Unrestricted Scientific Misinformation* campaign not only obscured the artificial nature of SARS-CoV-2 but also led to misjudgements by individuals, governments, policy makers, or even investors, leading to greater medical, social, and economic disorders.

Importantly, this campaign is still ongoing. More "novel" animal coronaviruses are going to be published by the CCP-influenced individuals and laboratories and thereby continue to build the falsified theory of SARS-CoV-2 having a natural origin. Similarly, the CCP will continue to use scientists under its control and influence, who often hold high titles, to try to control the narratives using these fraudulent publications.

At the same time, Dr. Yan remains committed to revealing the truth of SARS-CoV-2 to the world. Honest discussions that are based on scientific facts and logic are always welcome by Dr. Yan. Dishonest and intentionally misleading arguments, like these two "reviews", will be exposed as demonstrated in this document. Dr. Yan is open for live debates on any influential platform with any scientist(s) who support the natural origin theory and/or believe that China is not where SARS-CoV-2 originated. Dr. Yan and us co-authors will also produce additional report(s) providing our analyses on important aspects of COVID-19. We sincerely hope that our reports, both published and upcoming, would be treated with seriousness that they deserve. We suggest so because we believe the truths in our reports can not only help the global fight against COVID-19 but also awaken the world to take actions to prevent future *Unrestricted Bioweapon* attacks.

Ultimately, the realization of SARS-CoV-2 being an *Unrestricted Bioweapon* and the current pandemic an *Unrestricted Biowarfare* makes it clear that the CCP regime is the one responsible for this brutal attack on humanity. The CCP government must be held accountable. If not, it can only be encouraged to commit more crimes and continue to hurt the global community.

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Part I:

Point-to-Point Responses to the *MIT Press* "Reviewers"

These reviews are now openly published, along with a response from the **RR:C19 Editorial Office**, that states, "Collectively, reviewers have debunked the authors' claims that: (1) bat coronaviruses ZC45 or ZXC21 were used as a background strain to engineer SARS-CoV-2, (2) the presence of restriction sites flanking the RBD suggest prior screening for a virus targeting the human ACE2 receptor, and (3) the furin-like cleavage site is unnatural and provides evidence of engineering. In all three cases, the reviewers provide counter-arguments based on peer-reviewed literature and long-established foundational knowledge that directly refute the claims put forth by Yan *et al*. There was a general consensus that the study's claims were better explained by potential political motivations rather than scientific integrity."

Overall response to the "reviewers" at the MIT press:

We disagree with the "reviewers" or the editor soliciting these "reviews" on their conclusion. In fact, none of the arguments offered by the reviewers stands on solid grounds. The so-called evidence that they used to support their claims has been proven to be fraudulent[1]. The reviewers also showed severe deficiencies in their understanding of coronavirus biology and evolution. Their comments are baseless, careless, and misleading. As a result, their reckless behaviors have damaged the world's efforts in revealing the true origin of COVID-19. They were the ones lacking scientific integrity, not authors of the Yan reports. In fact, the Yan reports continue to stand strong because they are based on solid facts, logical and robust analyses, and scientific integrity.

Also, the reviewers baselessly stated that our report can be "explained by potential political motivations" and questioned the timing of our publication. However, the truth is the opposite: our report was not about politics but about the scientific investigation of the true origin of the COVID-19 pandemic. The ones that are politicizing the issue are these "reviewers" led by Dr. Robert Gallo. Instead of focusing on discussing the science of our scientific report, they went out of their ways as "peer reviewers" and brought in issues that have nothing to do with science. The timing of our report was not calculated. However, it is interesting that, when the "reviewers" questioned the timing of our report, their "review" was published only ten days after our publication. This is an unbelievable speed in the world of peer review. One has to wonder what is behind the timing of the rushed publication of this "review" and what are the motivations of these "reviewers".

It has to be pointed out that Dr. Gallo, the leading "reviewer" here, has close ties to the Chinese Communist Party (CCP) government. In 2009, an institute named the *Gallo Virology Institute* was established in Jinan, Shandong Province[2]. Dr. Gallo also has business and financial ties in Hong Kong since 2017[3]. Furthermore, the CCP government has very recently awarded Dr. Gallo the *VCANBIO Award for Biosciences and Medicine*[4], which is, according to the news report, "*a significant and authoritative award in the life sciences and medicine field of China"*. It is very interesting that the award was announced three months after Dr. Gallo published this review criticizing and defaming our report.

Although we are not obligated to respond to these biased and scientifically weak comments, we do feel that responses from us would be valuable in preventing further damage that these "review" comments might cause. In the end, it is the true origin of COVID-19 that we want the world to understand. We have therefore provided point-to-point responses below. For distinction, our responses are in black, while the reviewers' comments are in blue. References added by us are grouped at the end of *Part I*, also in black.

Review 1 by Takahiko Koyama

RR:C19 Evidence Scale rating by reviewer:

- **Misleading.** Serious flaws and errors in the methods and data render the study conclusions misinformative. The results and conclusions of the ideal study are at least as likely to conclude the opposite of its results and conclusions than agree. Decision-makers should not consider this evidence in any decision.

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Review:

COVID-19 caused by SARS-CoV-2 has damaged economies of nations in unprecedented degree and the virus has exposed the fragilities and vulnerabilities of our society against novel pathogens. Therefore, the origin of the virus needs to be identified promptly and unambiguously to prevent further damages and future occurrences of similar pandemics. Unfortunately, as of today, we have not identified viable intermediate host candidates for SARS-CoV-2, yet. In this manuscript "Unusual Features of the SARS-CoV-2 Genome Suggesting Sophisticated Laboratory Modification Rather Than Natural Evolution and Delineation of Its Probable Synthetic Route", authors have implied that SARS-CoV-2 is engineered rather than naturally emerged. Such possibility should not be ruled out if compelling scientific evidences are exhibited.

The authors claim that SARS-CoV-2 was engineered from CoV ZC45, which was obtained from a bat sample captured in Zhoushan in 2017[1]. A variant analysis with respect to SARS-CoV-2 is performed and over 3000 genomic differences are identified between ZC45 and SARS-CoV-2 genomes. Authors need to explain how these differences are engineered in a similar manner to their argument in spike protein with specific restriction enzymes utilized. In practical point of view, ZC45 cannot be a template and authors need to find a better template.

Furthermore, authors' speculation of furin cleavage insert PRRA in spike protein seemed quite interesting at first. Nevertheless, recently reported RmYN02 (EPI_ISL_412977), from a bat sample in Yunnan Province in 2019, has PAA insert at the same site[2]. While the authors state that RmYN02 is likely fraudulent, there are no concrete evidences to support the claim in the manuscript. In addition, argument of codon usage of arginine in PRRA is not convincing since these are likely derived from some kind of mobile elements in hosts or other pathogens. Further investigations are necessary to unravel the mystery of the PRRA insert.

For these reasons, we conclude that the manuscript does not demonstrate sufficient scientific evidences to support genetic manipulation origin of SARS-CoV-2.

References

1. Hu D, Zhu C, Ai L, He T, Wang Y, Ye F, et al. Genomic characterization and infectivity of a novel SARS-like coronavirus in Chinese bats. Emerging microbes & infections. 2018;7(1):154-. doi: 10.1038/s41426-018-0155-5. PubMed PMID: 30209269.

2. Zhou H, Chen X, Hu T, Li J, Song H, Liu Y, et al. A Novel Bat Coronavirus Closely Related to SARS-CoV-2 Contains Natural Insertions at the S1/S2 Cleavage Site of the Spike Protein. Curr Biol. 2020;30(11):2196-203.e3. Epub 2020/05/11. doi: 10.1016/j.cub.2020.05.023. PubMed PMID: 32416074.

Response to Review 1:

The reviewer asked for an explanation of how other parts of the genome could be engineered in a similar way as the Spike engineering – using restriction enzyme digestion. Clearly, this reviewer failed miserably in understanding our report. We have never said in the report that other parts of the genome of SARS-CoV-2 were also engineered using restriction enzyme digestion. In fact, in part 2 of our first report[5], particularly in section 2.2 step 4, we have clearly described how other parts of the genome should have been incorporated without the need of restriction enzyme digestions:

"*In addition to the engineered spike gene (from steps 1 and 2) and the ORF1b gene (from step 3), other fragments covering the rest of the genome would be obtained either through RT-PCR amplification from the template virus or through DNA synthesis by following a sequence slightly altered from that of the template virus. We believe that the latter approach was more likely as it would allow sequence changes introduced into the variable regions of less conserved proteins, the process of which could be easily guided by multiple sequence alignments. The amino acid sequences of more conserved functions, such as that of the E protein, might have been left unchanged.*"

The mistake that the reviewer made here indicates that he either did not understand the relevant section of the report or he intentionally ignored this section when giving his comments. In either case, he has proven himself as an unqualified reviewer.

In the final remarks section of our second report[1], we further described how changes could be introduced and why such changes are necessary in the making of a bioweapon:

"*As illustrated in our earlier report, although a template virus was used, the creation of SARS-CoV-2 must have involved introducing changes to the template sequence through DNA synthesis (steps 1 and 4 in part 2 of our earlier report). Such a practice can be safely guided by multi-sequence alignment of available SARS and SARS-like coronavirus sequences. The process of this practice has been illustrated[115], and both syn mutations and amino acid (non-syn) mutations at variable positions/regions would be introduced. From the perspective of the responsible scientists, these changes are necessary because, otherwise, the engineered nature of the virus and its connection to its template would be evident.*"

The reviewer also argued that ZC45 could not be used as a template in the creation of SARS-CoV-2. The reviewer's comment here is mistaken and irresponsible. An important fact here is that, although ZC45/ZXC21 and SARS-CoV-2 are 89% identical on the nucleotide level, their sequence identity on the amino acid level is 95%. Apparently, over 50% of these changed nucleotides are synonymous mutations that do not alter the identity of the encoded amino acids. The remaining differences, which are non-synonymous mutations, could easily be introduced into variable regions/positions of proteins. Again, this process has been nicely illustrated in the supplementary figure 1 of a 2008 publication[6]. Finally, a small number of random mutations must have also accumulated during the subsequent laboratory developments as some downstream processes mimic natural evolution to a certain extent. These random mutations should have contributed to this overall divergence as well. Therefore, the apparent divergence between ZC45/ZXC21 and SARS-CoV-2 does not preclude ZC45/ZXC21 from being used as the template for the creation of SARS-CoV-2.

Importantly, we have shown in our report that 1) SARS-CoV-2 and ZC45/ZXC21 share 100% identity on the E protein and 2) the E protein is tolerant of amino acid mutations as evidenced in both bat coronaviruses and in the SARS-CoV-2 strains. If the virus has evolved naturally and jumped from bats first to intermediate host(s) and then to humans, how could the SARS-CoV-2's E protein remain 100% identical to that of the ancestor bat virus? The fact that this reviewer failed to recognize the significance of this evidence in our report should be noted in assessing the credibility of this review.

Furthermore, it is important to recognize that, when what is being created is a bioweapon, the perpetrators would understandably want to blur the connection between the bioweapon and the template used for its creation. The ~11% differences at the nucleotide sequence or ~5% differences at the amino acid level are necessary from their perspective.

It is also important to realize that some of these changes may have been introduced with an intention to enable other designed functions, although these intended functions may or may not have fully materialized in the final version of the virus. We will publish future reports investigating such possibilities.

Concerning RmYN02 and the furin-cleavage site, the reviewer needs to explain in details how the PRRA insertion can be derived through mobile elements in hosts or other pathogens. The one sentence comment he provided here has no scientific strength and therefore does not constitute a valid argument. We recommend the reviewer read our reports carefully and learn how to analyze a scientific problem properly. Only then he can respond adequately and responsibly and thereby possibly qualify as a reviewer here.

Finally, RmYN02 is fraudulent as explained in our second report[1]. In our first report, we have described RmYN02 as fraudulent and stated that we will publish a second report providing the evidence of its fabrication. The reviewer should not have rushed (ten days after the publication of our first report) to use RmYN02 as his evidence in making his comment.

Overall, the arguments made by this reviewer do not stand scientifically at all.

Review 2 by Adam Lauring

RR:C19 Evidence Scale rating by reviewer:

- **Misleading.** Serious flaws and errors in the methods and data render the study conclusions misinformative. The results and conclusions of the ideal study are at least as likely to conclude the opposite of its results and conclusions than agree. Decision-makers should not consider this evidence in any decision.

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Review:

The main issue with this manuscript is that it is not "scientific." In presentation, it reads like an opinion piece. The authors tie various threads together into a story. However, they are only able to do this by focusing on the most sinister interpretation of just a subset of evidence. Much data is ignored or discounted. Perhaps most important, the argument or hypothesis made by the authors is neither provable nor falsifiable. This falsification principle is a key tenet of science.

Overall response to Review 2:

It is nothing short of a lie that this reviewer described our report as "not scientific". As evidenced from his specific comments below, this reviewer failed to provide any solid scientific evidence or argument and yet repeatedly used similar degrading terms to label our report. The strong bias of his could not be more evident. His behavior here is reckless not only because peer review is supposed to be done in an unbiased manner but also because his irresponsible comments have misled the world's efforts in tracing the true origin of COVID-19.

The reviewer commented that we have intentionally ignored "much data". Evidently, the reviewer is referring to publications reporting RaTG13, pangolin coronaviruses, and the RmYN02 bat coronavirus. All of these viruses have been proven to be fraudulent in our second report[1]. It is clear that Dr. Lauring's opinion was built upon these fabricated evidence and data, which dictates that his judgements/comments here are practically baseless and therefore not credible.

The reviewer is also wrong in stating that our argument or hypothesis is neither provable nor falsifiable. In part 2 of our report, we have described a postulated synthetic pathway for the laboratory creation of SARS-CoV-2. There, all steps were proposed with strong support from the literature, indicating that these experiments have all been carried out in the coronavirus research labs in recent years and the proposed methods are the preferred ones that are still popular in the field[7,8]. Therefore, our hypothesis is entirely provable and falsifiable by research labs having such capacities. The inability to recognize this fact speaks strongly of Dr. Lauring's lack of quality as a reviewer and a scientist in general.

Additional questions posed by the editorial office:

1. Does the manuscript confirm previous work or refute current understanding?

It does not. The manuscript attempts to refute our current understanding of the origins of SARS-CoV-2. Briefly, the consensus is that SARS-CoV-2 is a zoonosis and originated in bats with perhaps an intermediate host before spilling over into humans. The authors of this manuscript argue instead that SARS-CoV-2 was engineered in a laboratory starting from a bat coronavirus sequence. They are selective in their citation of the literature. They discount several peer reviewed studies that have provided evidence for the natural origins of SARS-CoV-2. They claim that some of these are not worthy of consideration, because of conflicts of interest from the authors. It is not clear what those conflicts of interest are and why those studies should not stand. They also offer "evidence" that calls these papers into doubt. However, the citations do not appear to substantially call these papers into question. Some appear to be preprints that are more opinion pieces or conjecture, much like this one. To put it another way, the authors don't contest the natural origin hypothesis with data. Instead, they offer ideas and opinions.

Response: As stated in our report, the reason we were selective in trusting published work was because some recent publications were clearly reporting fabricated coronaviruses[9-14] and some other publications have based their arguments on these fabricated data[15,16]. In fact, we have published our second report debunking these fabrications, which further disproves the natural origin theory that these fabrications meant to support[1].

Contrary to the reviewer's comment, we have clearly specified conflict of interests of individuals involved in publishing the unfounded opinion piece, "*The Proximal Origin of SARS-CoV-2*"[15]. Specifically, among these authors, Dr. Ian Lipkin has been working with the CCP government since 2003. He has been honored by the CCP government with several prestigious awards[17,18], including one given to him in January 2020[17],

not too long before the publication of his misleading *Nature Medicine* opinion piece. Dr. Edward Holmes, another co-author of this article, has also been working closely with the CCP laboratories, including publishing two articles reporting fabricated pangolin coronaviruses and the RmYN02 bat coronavirus, respectively[9,13]. It is noteworthy that two publications of fabricated pangolin coronaviruses (only one of them involves Holmes) were done in collaboration with scientists from the *Academy of Military Medical Sciences* (AMMS)[9,11,19,20]. Dr. Holmes also holds two visiting/guest professor positions in China, one at Fudan University and the other at the Chinese Center for Disease Control and Prevention[21]. These conflicts of interests are factual and substantial. In addition, this influential *Nature Medicine* publication relied heavily on the fabricated viruses to form its argument for a natural origin of SARS-CoV-2[15]. It is both appropriate and necessary to exclude it in any valid analysis of the origin of SARS-CoV-2.

Our citations were inclusive (peer-reviewed, preprint, etc) and were chosen based on their scientific values rather than their formats. It is also important to realize that all the fabricated coronaviruses were published as peer-reviewed articles on top scientific journals[9-14], highlighting the possible disconnection between peer reviewed publications and scientific truth. Furthermore, it is proven that an influential, peer-reviewed publication on a reputable journal can be fraudulent and later retracted[22-26]. Therefore, peer-reviewed publication does not automatically guarantee scientific merits or integrity. What is especially relevant and noteworthy is that manuscripts dissenting from the natural origin theory of SARS-CoV-2 have clearly been censored[27].

Finally, in our report, we have provided in-depth analyses on the genomic sequences of relevant viruses. Our conclusion was drawn based on substantial genetic evidence and analyses. Describing our evidence-based reasoning and analyses as just ideas and opinions is therefore counterfactual and dishonest. It is a great shame that Dr. Lauring is so awfully deficient in his capacity as a reviewer and yet functioned in this role regardless.

2. How well does the manuscript position the work within the current literature/understanding?

As above, citations are selective and the authors dismiss available data and literature without trying to work within it. The evidence for a remote or recent bat origin of SARS-CoV-2 is supported by the following manuscripts:

Andersen et al. Nature Medicine, 10.1038/s41591-020-0820-9
Lam et al. Nature 2020, 10.1038/s41586-020-2169-0
Latinne et al. Nature Communications doi.org/10.1038/s41467-020-17687-3
Xiao et al. Nature doi.org/10.1038/s41586-020-2313-x
Yan et al. Current Biology doi.org/10.1016/j.cub.2020.05.023
Boni et al. Nature Microbiology doi.org/10.1038/s41564-020-0771-4

Response: In fact, these publications listed by the reviewer are exactly what we have intentionally excluded due to their fabricated and/or misleading nature[1]. Among them, three were directly reporting fabricated coronaviruses[9,11,13] (the reviewer also made an error in the *Current Biology* publication as the first author should be Zhou, not Yan). The other three articles the reviewer listed have all based their phylogenetic analyses on the fabricated viruses. In fact, not only these publications should be excluded from our report, but also they should be excluded from all phylogenetic analyses that wish to sustain future validations. The reviewer's approach, putting a blind trust on publications that are clearly fraudulent according to the overwhelming evidence, is wrong and irresponsible, especially in facing the pressing issue of the COVID-19 pandemic.

Additional areas in which the work does not fit with the current science.

(a) The authors speculate - without evidence - that SARS-CoV-2 was engineered from the backbone of ZC45 or ZXC21 bat coronaviruses. This appears to be convenient for their argument, as these viruses have some linkage, per the authors, to the Chinese government or military. As others have pointed out, using these as starting points for genetic engineering makes little sense. These viruses differ from SARS-CoV-2 at approximately 10% of the positions in the genome. If someone were to engineer a virus like SARS-CoV-2, they would start with a more closely related virus. It is much simpler.

Response: Contrary to the reviewer's comment here, in our report, we have laid out the evidence supporting that ZC45/ZXC21 should be used as the template. Part of the evidence was the 100% identity on the E protein between ZC45/ZXC21 and SARS-CoV-2. The reviewer should offer his evidence-based, logical counter-argument against this before he could argue that ZC45/ZXC21 was not used as the template. This empty comment of his weighs next to nothing in front of the relevant evidence and analyses provided in our report.

About the 10% divergence between ZC45/ZXC21 and SARS-CoV-2, we have elaborated extensively in our response to review 1 and will not repeat here again. In addition, the reviewer here ignores the simple logic that creation of a bioweapon also bears the burden of hiding its template and thus its creators. Having a product closely resembling the original template is something they would avoid as much as possible. This is common sense, which is unfortunately missing in the reviewer's mind.

(b) The authors attach inordinate significance to a restriction enzyme site near the receptor binding domain. They consider it something of a smoking gun as it will allow for sub cloning of receptor binding domains during the engineering process. This site is a 6 nucleotide recognition sequence and would occur by chance once every 4096 bases in a genome sequence. In SARS-CoV-2, which is approximately 30,000 bases, one would expect to find this particular sequence 7-8 times by chance. Therefore, attaching significance to its existence in the genome does not make a lot of scientific sense.

Response: This comment showcased the biased and sinister nature of the reviewer's mindset in carrying out this "review". The reviewer took our argument on the restriction sites out of its significant context and thereby "justified" his criticism.

First, we have offered our analyses proving that the receptor-binding motif (RBM) of SARS-CoV-2 could not be derived from natural evolution. To argue the opposite, the reviewer needs to first come up with an evidence- and logic-based rebuttal and prove how natural evolution could be responsible for the emergence of such a RBM in SARS-CoV-2. However, this essential element could not be identified in the reviewer's argument here.

Second, EcoRI and BstEII sites are located exactly at where Dr. Zhengli Shi and Dr. Fang Li (Shi's long-term collaborator and an expert in the structure biology of Spike-ACE2 interactions) used restriction enzyme digestion to swap the RBM[7,28].

Third, the EcoRI and BstEII sites are unique in the *spike* gene. No other EcoRI or BstEII sites are available in the *spike*, which makes a RBM swap extremely convenient.

Fourth, these two sites are unique only to the SARS-CoV-2 *spike* and are not present at the corresponding locations of any other coronavirus' *spike* gene. Importantly, the "introduction" of an EcoRI site has changed a conserved amino acid from Threonine to Serine. Except for SARS-CoV-2 and the fabricated coronaviruses published after the outbreak[29], no other coronaviruses have a Serine at this particular location and all contain a Threonine instead.

These circumstances are substantial and key in enabling us to describe the existence of EcoRI and BstEII sites at either end of the SARS-CoV-2 RBM as the "smoking gun" and indicative of genetic manipulation. The reviewer is fully aware of this context as it was thoroughly described in our report. However, he left this significant context out intentionally so that he could call our conclusion here as "does not make a lot of scientific sense". The bias of his cannot be more evident.

(c) The furin-like cleavage site is also considered highly suspicious to the authors. It should be noted that many viruses have these cleavage sites. In and of itself, its existence is not evidence for an engineered origin for SARS-CoV-2. See for example Yan et al. Current Biology (doi above)

Response: In our report, we have fully acknowledged that "*furin-cleavage site at this location (S1/S2 junction) has been observed in other groups of coronaviruses*". However, we have also emphasized that such a site is completely absent naturally in the lineage B of β coronaviruses (excluding SARS-CoV-2 and the fabricated ones), which the reviewer bluntly ignored in his comment here. One of our arguments is that "*certain selective pressure seems to be in place that prevents the lineage B of β coronaviruses from acquiring or maintaining such a site in nature.*" We continue to stand with this argument as it is factual and accurate.

Our conclusion was also based on the fact that the rare codon, CGG, was used in tandem to code the two adjacent Arginine residues within the inserted -PRRA- sequence, which is essential in constituting the furin-cleavage site. In addition, a FauI restriction site is also formulated by the codon choices here. This evidence is indispensable in our conclusion that genetic manipulation should be responsible for the insertion of the furin-cleavage site. However, the reviewer left it out in his argument, which, once again, speaks against his qualification as a competent, unbiased reviewer here.

The article[13] that the reviewer suggests to be supportive of the natural origin of the furin-cleavage site is one that is proven fraudulent in our second report[1]. He also repeated his mistake in stating the first author's last name incorrectly[13].

Furthermore, introducing human protease cleavage site into the Spike protein of coronaviruses to enable cross-species transmission into human population is a concept well-known to Drs. Zhengli Shi and Fang Li[30] (reference #50 in our report[5]). In fact, in 2015, they have already acquired the most essential knowledge in Spike engineering:

"*Viral adaptation to human cellular proteases is critical for viral infection of human cells because human cellular proteases, particularly endosomal proteases, are more reliable sources than some extracellular proteases to activate viral entry. Previous research also identified two mutations in SARS-CoV spike that led SARS-CoV to transmit from palm civets to humans. These mutations increased the capability of SARS-CoV spike to bind human receptor angiotensin-converting enzyme 2. Thus, different entry factors appear to have played the most critical roles in the cross-species transmission of MERS-CoV and SARS-CoV: adaption to human cellular proteases by MERS-CoV and adaption to human receptor by SARS-CoV.*" [30]

Intriguingly, this understanding by the above experts has been precisely mirrored in the reality of SARS-CoV-2 Spike – it has a designed/engineered RBM and an inserted human protease-cleavage site.

Clearly, the genetic evidence identified in the *spike* of SARS-CoV-2, which concerns both the RBM and the furin-cleavage site, respectively, match precisely these scientists' deep understanding and extensive experience in Spike engineering.

(d) The proposed route to engineering SARS-CoV-2 as diagrammed in Figure 8 is simply not credible. If there were a sophisticated effort to engineer SARS-CoV-2 in a laboratory, this would not be the route. Entire viral and bacterial genomes have been created by gene synthesis. That would be the route, as opposed to the multistep restriction enzyme cloning strategy outlined by the authors (see also the significance attached to EcoRI restriction site in my comment above).

Response: The reviewer is suggesting that the creation of a highly efficient, weaponized viral pathogen can be done through gene synthesis based on an entirely designed genome. This comment, however, is devoid of scientific vigor.

Is there any literature evidence or real-life example that a novel virus, produced based on an entirely computer-designed and synthesized genome, can recognize human receptors optimally and over the receptor of any other animals? Has such a designed virus ever caused a global pandemic? Without providing such evidence, the reviewer is only showing his ignorance in science here by making the above comment.

The reviewer does not seem to understand that virology is more of an experimental science. So far, all of the gain-of-function work done in the coronavirus area involved testing of designed constructs in wet labs. The efficiency of infection and many other aspects of a novel, artificial virus have to be tested and sometimes selected for. The overall success can be maximized through a step-wise process, where each key function would be ensured and likely optimized at a particular step. In many (if not all) of these steps, the optimal variant(s) would be selected over other candidates and carried over to the next stage of development.

Contrary to the reviewer's description of "not credible", our postulated route as illustrated in Figure 8 of our report was fully supported by literature. We have provided references for each step, showing that the exact techniques have been used by experts in the coronavirus field. More importantly, the sequence of these steps is logical and consistent with what is typically followed in such gain-of-function work.

(e) A complete review of the many issues with this manuscript can be found here. I concur with the assessments of these authors. https://www.centerforhealthsecurity.org/our-work/publications/in-response-yan-et-al-preprint-examinations-of-the-origin-of-sars-cov-2

Response: The review provided by Warmbrod et al. from *Johns Hopkins Center for Health Security* is of extremely poor quality. We have also included our point-to-point responses to these reviewers in the next section (part II) of the current writing. It is unfortunate that this reviewer concurs with Warmbrod et al., although we are also not surprised given that both parties are similarly biased and miserably incompetent as reviewers and scientists.

3. Is there clarity regarding the recommended actions the result from the findings?

In this reviewer's opinion, no. The manuscript does not make its case from the foundation of sound scientific argument. It is therefore not accurately presented and does not speak to key audiences.

Response: As demonstrated in his above comments, this reviewer has fatal deficiencies in his capacity as a reviewer here. Needless to say, this judgement of his carries no weight.

4. Do the authors pay attention to ethics, diversity, and inclusion?

A key aspect of research ethics and the responsible conduct of research is to include information on who supported the work - financially or otherwise. The authors' affiliation is the "Rule of Law Society & Rule of Law Foundation." It is not clear who supports this Foundation or what its purpose is. It is important for there to be transparency regarding research support, especially for a manuscript that is based on conjecture as opposed to data or empiricism. It is also unethical to promote what are essentially conspiracy theories that are not founded in fact.

Response: The work was led by Dr. Li-Meng Yan and done collaboratively by a group of scientists, who are experts in their respective fields. Except for Dr. Yan, the co-authors are using pseudonyms. This work did not require any wet laboratory experiments or cost. The analyses were all based on publicly available data and literature and were done by all authors voluntarily in their spare time. Our work is independent; except for the authors, no one else was involved in or has altered our report in any way.

~~The affiliation to the *Rule of Law Society & Rule of Law Foundation* was chosen because we want to express our gratitude toward these organizations for having helped Dr. Yan escape the life-threatening situations she faced in Hong Kong. At the time of her escape at the end of April in 2020, her personal safety was under jeopardy because her revelation of the true origin of SARS-CoV-2, which started in January 2020, had caught the attention of the Chinese Communist Party (CCP) government. The two organization had provided financial support for Dr. Yan's flight from Hong Kong to the US and for her initial settlement here.~~

(*Comments on July 17th, 2021*: Because the ROLF & ROLS unilaterally requested to have our reports closed, which violated the rules of scientific publications, we have changed our affiliation in responding to this situation. Relevant contents in the above paragraph were crossed out because we believe our earlier views on this matter were misled and such descriptions do not truthfully reflect real events.)

Contrary to Lauring's blame here, our conclusions were drawn from comprehensive, logical, and in-depth analyses, which were based on substantial available data and evidence. The inability to acknowledge these facts showed once again the severe lack of quality of Lauring as a scientist and a reviewer.

Review 3 by Robert Gallo

RR:C19 Evidence Scale rating by reviewer:

- **Misleading.** Serious flaws and errors in the methods and data render the study conclusions misinformative. The results and conclusions of the ideal study are at least as likely to conclude the

opposite of its results and conclusions than agree. Decision-makers should not consider this evidence in any decision.

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Reviewer Comments:

I) Widely questionable, spurious, and fraudulent claims are made throughout the paper about the thought-to-be precursor of SARS-2, RaTG13, found in bat caves. The author's attacks include quotes which have not been referenced, including how this "has been disputed and its truthfulness widely questioned. Soon a paper proving that will be submitted." She then goes on to attack several genome sequences as fraudulent, ranging from pangolin coronaviruses to bat coronaviruses, again without evidence. The reference she cites for that, in fact, does not make that claim.

Response: We disagree completely with the reviewer. We have cited seven references in the introduction section when we described the fraudulent nature of the RaTG13 virus, which should, at the very least, caution the reviewer to not put a blind trust on RaTG13. In addition, to help people fully understand the fraudulent nature of RaTG13 and other viruses fabricated by the CCP-controlled labs, we have published our second report on October 8th, 2020, where we provided substantial evidence and analyses to support and prove our claims[1]. Gallo should not have rushed to blindly support RaTG13 and thus the natural origin of the virus. This behavior of his is highly unprofessional and irresponsible.

Importantly, the overwhelming evidence presented in our second report irrefutably proved that the above-mentioned coronaviruses are all fraudulent. Clearly, it is the reviewer's comment here, not our report, that is "questionable, spurious, and fraudulent". If Dr. Gallo disagrees, we welcome him to challenge the findings in our second report with evidence-based, logical analyses and reasoning.

II) In her killing off of RaTG13 (without a shred of evidence or logic) she brings in her favorite "horse," ZC45, but I do not understand why she chooses this except that it has connections to the Chinese military. She wants this candidate to be the backbone of SARS-2. This "military" virus she writes about as the real predecessor of SARS-2 is over 3,000 nucleotides different from SARS-2. This is a long way off.

Response: Again, we disagree with the reviewer as we have provided sufficient literature evidence in our report regarding RaTG13. We also have published our second report, which presented, in great details, various evidence proving the fraudulent nature of the RaTG13 virus.

More importantly, we have reasoned extensively and in great depth on why ZC45/ZXC21 or a closely related bat coronavirus must be the backbone/template used for the creation of SARS-CoV-2. Part of it was based on the evidence that SARS-CoV-2 and ZC45/ZXC21 are 100% identical on the E protein. We have proved that the coronavirus E protein is tolerant of mutations and the SARS-CoV-2 E protein has seen mutations shortly after the virus started circulating in the human population. How could such a protein sequence be preserved 100% during natural evolution when the virus must have evolved extensively previously and have jumped the species barrier multiple times? This is simple logic based on clear and straightforward virological facts. The inability of Dr. Gallo to correctly weigh these facts is a shame.

In addition, although on January 19th, 2020, Dr. Yan for the first time revealed that ZC45/ZXC21 are the template used for the creation of SARS-CoV-2[31], there are other indications too. In the very first

publication reporting the novel SARS-CoV-2 virus on January 21st, 2020, a group of Chinese scientists intentionally left out ZC45 and ZXC21 in their polygenetic analysis of the SARS-CoV-2 evolution[32]. This was the time when the fabricated RaTG13 virus had not been published and ZC45/ZXC21 were, by any means, the closest relatives of SARS-CoV-2[33]. The intentional omission of ZC45 and ZXC21 by this group of Chinese virologists was clearly an effort to cover up the connection between SARS-CoV-2 and ZC45/ZXC21.

It is also worth mentioning that two *Nature* papers were published simultaneously on Feb 3rd, 2020, both reporting the first genomic sequence of SARS-CoV-2[14,33]. However, while Dr. Zhengli Shi's article that also reported RaTG13 became one of the most cited in the field and the foundation of the natural origin theory[14], the other *Nature* article, which revealed ZC45/ZXC21 as the closest relatives to SARS-CoV-2, has largely been ignored in the origin discussion[33]. The "importance" of publishing a fabricated RaTG13 virus to influence or control the narratives in the origin debate is, once again, evident.

In regard to the reviewer's comment on the over 3,000 nucleotide difference between SARS-CoV-2 and ZC45/ZXC21, detailed explanations have been provided in our response to review 1 and will not be repeated here again.

Therefore, clearly, it is these facts that led us to safely conclude that SARS-CoV-2's laboratory creation must have involved the Chinese military, not the other way around. *The question now becomes: what has led Gallo to the assertion that it must not have anything to do with the Chinese military?*

III) She then provides a complex scheme for converting ZC45 into SARS-2. God knows why. All one has to do is synthesize that sequence of SARS-2. Of course, this leaves one wondering how the satanic scientists would know in advance that SARS-2 would be so dangerous.

Response: This is a self-contradictory comment. Here, the reviewer has essentially admitted that the pathway he proposed, which is to "*synthesize that sequence of SARS-2*", is not practical. In our response to review 2, we have elaborated why it is ridiculous to propose that one can artificially create a novel, optimally human-targeting, pandemic-inducing virus based only on computer design and DNA synthesis. We will not repeat the details of our explanation here again.

However, it is important to point out that this comment showcased how irresponsible this reviewer is. Apparently, his questioning of our postulated route for the lab creation of SARS-CoV-2 is baseless; he did not provide any scientific evidence supporting his judgement. At the same time, he trashed his own proposal immediately in the next sentence. Dr. Gallo is abusing his role as an infectious disease expert here. People must have hoped that Gallo would offer his responsible judgements on this important issue and yet he did the very opposite.

IV) And how would the Chinese protect themselves? Well, according to the paper, the military knew it could be stopped by remdesivir. I would surely not want to be in the Chinese military if they were that naive.

Response: How would the Chinese people protect themselves? Under the ruling of the CCP, they could not. As we have stated in our second report, "*(t)he current pandemic is an attack on humanity*" and the Chinese people were no exceptions. In fact, they were the ones attacked and victimized first by this artificial pathogen.

Here, the reviewer distorted the relevant section of our report in making his comment. We have never stated that the Chinese military knew that remdesivir could block SARS-CoV-2 infection. In section 2.1 of our report, we have provided two possible reasons for why an *RdRp* segment of RaBtCoV/4991 could be used in the construction of the SARS-CoV-2 genome. One of the possible reasons was that the responsible scientists could have seen a feature in this RdRp, which makes them believe that this RdRp could be more amenable for antiviral drug discovery.

It is extremely unfortunate that the reviewer distorted our descriptions so severely in making this comment. Given the reviewer's accomplishments in the field of retrovirus biology, it is unlikely that he would misunderstand scientific writing to such a degree. It is more likely that Dr. Gallo did not treat the article under his review with the attention that is absolutely required from a peer reviewer. Such a behavior is reckless and irresponsible because the problem here concerns a world-wide pandemic caused by a deadly pathogen. It is an issue that deserves the ultimate respect from all scientists involved in the discussions.

V) The author also claims that the receptor binding domain (RBD) is suspiciously close to SARS-1. That is frankly untrue. The SARS-CoV-2 RBD sequence is nearly 100% homologous with that of the pangolin sequence —this is the reason she attempts to label the pangolin sequence data as also fraudulent.

Response: The reviewer again based his belief on fabricated data. As pointed in our first report[5] and proven in our second report[1], the pangolin coronaviruses were indeed fabricated. Therefore, the fact that the SARS-CoV-2 RBD is nearly 100% identical to that of the pangolin coronaviruses does not support a natural origin of this RBD. Rather, the fact that they had to falsify a natural origin for this RBD indicates that the opposite is true – this RBD must have been created artificially, which is consistent with the various evidence that we presented in section 1.2 of our first report[5].

Also contrary to the reviewer's argument, the way SARS-CoV-2 RBM resembles the SARS RBM is indeed suspicious. As described in section 1.2 and illustrated in Figures 3 and 4 in our report[5], all RBM residues crucial for hACE2 interaction have been "preserved", while majority of the non-essential residues have "mutated".

Note that our conclusion of this being suspicious is also based on the fact that the RBM of SARS-CoV-2 could not have been derived through natural evolution, which we have discussed extensively also in section 1.2 of our report. Furthermore, while a natural origin of SARS-CoV-2 RBM is not possible, evidence for artificial genetic manipulation is substantial (Figure 5 and associated discussions in our report), clearly indicating that the RBM must be a product of genetic engineering.

VI) She states that the furin cleavage sites do not occur in "other viruses of this class." By class, she means SARS-like. This is not true, as such sites are present in some coronaviruses and are subject to the whims of Mother Nature's evolutionary bent. In fact, MERS has two such sites and a chicken coronavirus also has two.

Response: The reviewer is behaving dishonestly here. Not only the words cited by the reviewer could not be found anywhere in our report, but also we have never hinted or described that this furin-cleavage site does not occur in "other viruses of this class". In fact, we have acknowledged in our report that "*furin-cleavage site at this location (S1/S2 junction) has been observed in other groups of coronaviruses*"[5].

What we have also stated was that *"(w)ithin the lineage B of β coronaviruses and with the exception of SARSCoV-2, no viruses contain a furin-cleavage site at the S1/S2 junction (Figure 6)"*[5].

Once again, Dr. Gallo has behaved dishonestly in making his comment here.

Furthermore, MERS and that chicken coronavirus are not SARS-like (lineage B β) coronaviruses, which is common knowledge of any virologist. Dr. Gallo's intentional omission of this fact here is misleading and speaks further against his credibility as a trustworthy reviewer.

VII) There is also the question of timing. Why is she "publishing" the paper now? Why hasn't she published before? Is it because it is election time? Why is she rushing to submit so soon? The research is backed by Steve Bannon! I question her credibility.

Response: This comment is not scientific. In peer review, it is of pivotal importance that the evaluation or judgement of the article is based solely on its scientific merits. Dr. Gallo had once again crossed the line and behaved irresponsibly in his role as the "peer reviewer".

We have never calculated the timing for our publication. As experts in our respective fields, we authors share the scientific judgement that SARS-CoV-2 is a lab-made, weaponized virus. We were also saddened by the fact that the natural origin theory, although baseless, is dominating in the scientific world as a result of a large-scale misinformation campaign. This was what had driven us into working toward a preprint article. Our analyses and writing, which were done carefully because we are fully aware of the seriousness of the issue, had progressed gradually and naturally until the manuscript had matured to publication quality. In fact, we wish we had published our report earlier and had brought what we believe is the truth to the world sooner.

What is actually interesting is the timing of this review by Dr. Gallo and his fellow "reviewers" – their review was published only ten days after the publication of our report[34]. What is also interesting was the timing of Dr. Gallo's recent award from the CCP government. On Dec 20th, 2020, three months after Dr. Gallo published this review criticizing our report, the CCP government honored him with the *VCANBIO Award for Biosciences and Medicine*[4]. However, Dr. Gallo's connection to the CCP goes long way back and beyond just awards. In 2009, the *Gallo Virology Institute* was founded in Jinan, Shandong Province[2]. Dr. Gallo also has business ties in Hong Kong[3]. These conflicts of interests speak strongly against Dr. Gallo's credibility as a peer reviewer here.

Contrary to Gallo's claim here, Dr. Yan's credibility and the timing of her actions are unquestionable. On January 19th, 2020, Dr. Yan then anonymously warned the world with the following messages[31]:

- The virus is transmitting from human to human.
- The CCP government is covering up the truth of the virus, including its human-to-human transmission and actual numbers of infections in Wuhan.
- The Huanan Seafood Market is a smokescreen and not where the virus originated.
- No intermediate, wild animal host exists.
- The virus will lead to a devastating pandemic if there is no timely and potent intervention.
- The virus is mutation-prone and new variants may emerge inevitably and rapidly.
- The virus is a bioweapon developed by the CCP government using the PLA-discovered ZC45/ZXC21 as the template.

Clearly, Dr, Yan's timely warnings then, like her other actions later, were all meant for protecting public health and for saving people's lives, not for politics. Also, these facts and assessments of Dr. Yan's had all been proven to be true.

Who is more credible than Dr. Yan on this issue?

Did Dr. Gallo ever deliver such truthful and helpful COVID-19-related knowledge to the public at this level of scale, with this much accuracy, and this early in time?

How much credibility does Dr. Gallo have here?

In reality, when the world was in a desperate need of the truth of the COVID-19 pandemic, Dr. Gallo abused his academic power and status and misled the world with a biased and dishonest review of the Yan report. He has proven himself a complete disgrace.

Finally, Gallo's assertion of a connection between our research and Mr. Bannon is untrue and extremely inappropriate. Our research was completely independent and not backed by Mr. Bannon or anyone else. The work was done exclusively by the scientist co-authors, and Mr. Bannon took no part in it whatsoever. There is also no financial link between us and Mr. Bannon.

However, it has to be mentioned that Mr. Bannon was one of the first people to have spoken the truth of COVID-19. Revealing the bioweapon nature of SARS-CoV-2 is crucial in the global fight against this harmful pathogen and in preventing future bioweapon attacks. In this sense, the actions of Mr. Bannon and many others who have described the true nature of COVID-19 to the public are honorable and deserve the recognition and appreciation from the public. In contrast, the actions of Gallo and the rest of these *MIT Press* "reviewers", which are dishonest and with a clear intention to mislead the public on the crucial issue of the COVID-19 pandemic, are absolutely shameful.

VIII) Finally, this paper should be used by teachers forever as a crystallized example of the "Gish Gallop". Alternatively, it could be used by editors to punish their most unfriendly reviewers.

Response: It cannot be more evident that Dr. Gallo's review comments here were all mistaken and/or dishonest. On the other hand, the science in our report has proven to be solid and irrefutable. "Gish Gallop" is a vivid description of the Gallo comments, but not of our report.

Review 4 by Marvin Reitz

RR:C19 Evidence Scale rating by reviewer:

- **Misleading.** Serious flaws and errors in the methods and data render the study conclusions misinformative. The results and conclusions of the ideal study are at least as likely to conclude the opposite of its results and conclusions than agree. Decision-makers should not consider this evidence in any decision.

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Review:

My thoughts on this report are that it is composed entirely of opinion and innuendo. Yan says she will be coming out with more concrete data later, but I doubt it, especially as this current report has been so long in coming. The timing is suspicious.

Response: It is very interesting that, while our report is irrefutably scientific with abundant evidence and analyses put together in a logical manner, all four reviewers here outrageously described our report as "not scientific" and/or just "opinions". At the same time, the four reviewers provided no valid scientific argument themselves and instead left only unsupported claims, which equal opinions. It is intriguing that the same mistake could be made by each of the four reviewers. This pattern is suspicious and should be investigated.

Consistent with this pattern, as evidenced below, multiple comments from reviewer 4 are essentially the same as those made by reviewer 3. This is a blunt violation of the rules of peer review as each reviewer is supposed to provide his/her unbiased, independent critical analyses of the manuscript.

The reviewer also commented that no more concrete data would come from us. Clearly, he had already been proven wrong as our second report, a concrete scientific article, was published on October 8th, 2020[1], only 14 days after their "review" was published[34] and only 24 days after the publication of our first report[5].

She modulates her description of the RaTG13 sequence from "widely questioned" moves to "spurious" moves to "likely fraudulent". The old camel nose/tent trick. See the following.

"However, the existence of RaTG13 in nature and the truthfulness of its reported sequence are being widely questioned6-9,19-21."

"A follow-up report, which summarizes the up-to-date evidence proving the spurious nature of RaTG13, will be submitted soon."

"What is not thoroughly described in this report is the various evidence indicating that several coronaviruses recently published (RaTG1318, RmYN0230, and several pangolin coronaviruses27-29,31) are highly suspicious and likely fraudulent."

She requires certain viral sequences (including RaTG13 and the pangolin viruses) that are closely related to SARS-CoV2 to be fraudulent, as it allows her to claim that her candidate virus, ZC45, is the closest relative to SARS-CoV2. Why is this her candidate? The reason is probably it's connection with military, see below.). RaTG13 is 97% identical at the nucleotide level, ZC45 only 89%. At least one of the sources she quotes for the pangolin sequence being fraudulent does not, in fact, make that claim. It merely says that the pangolins may have gotten the virus from a different species. And even if they were fraudulent, it still would require more than 3,000 nucleotide substitutions to become SARS-CoV2. This is not even slightly credible; it beggars reason.

"Genomic sequence analysis reveals that ZC45, or a closely related bat coronavirus, should be the backbone used for the creation of SARS-CoV-2."

"The genomic sequence of SARS-CoV-2 is suspiciously similar to that of a bat coronavirus discovered by military laboratories in the Third Military Medical University (Chongqing, China) and the Research Institute for Medicine of Nanjing Command (Nanjing, China) (i.e, ZC45)."

Response: We have published our second report which proved the fraudulent nature of these novel animal coronaviruses: RaTG13, RmYN02, and a series of pangolin coronaviruses. We assume that the reviewer had been misled by these fabricated viruses in making this comment here.

However, if the reviewer truly believes that these coronaviruses are not fabricated, he could only argue so scientifically — he would have to use in-depth analyses and valid supporting literature to prove his point, similar to what we have done in our second report[1]. Unsupported claims like what this reviewer is making here carry no weight.

In regard to the over 3,000 nucleotides difference between ZC45 and SARS-CoV-2, we have provided detailed explanations in our response to review 1.

Then she presents a scheme for converting ZC45 to SARS2. Totally unnecessary, all you would have to do is synthesize your desired genome, transfect the DNA into a host cell, and out pops your virus. The larger question is, how would you know what exact genome would have all the characteristics you wanted?

Response: This is essentially the same argument made by reviewer 3. Not only both reviewers argued that designed genome and DNA synthesis would be the go-to approach, but also they both immediately disproved their own proposal.

As we have explained previously in responding to review 3, it is simply ridiculous to propose that a novel coronavirus, which is optimal in infecting humans and can cause a pandemic, can be produced only through computer-design and DNA synthesis. Unless the two reviewers had the same brain or one had copied the idea from the other, it is impossible for them to have been so synchronized: making the identical, scientifically absurd proposal and then dismissing it immediately afterwards.

Her second point is that the RBD is "suspiciously close to that of SARS1. No it's not. The pangolin sequences are 100% in the RBD. Can't get much closer than that. That's why she has to claim the pangolin sequences are fraudulent.

Response: This is also essentially the same mistaken comment made by reviewer 3, which we have responded to earlier.

Point 3 is the furin cleavage site. She states that this doesn't occur in "other viruses of this class". Not clear what she means by class. Presumably she means SARS-like CoVs. It's certainly in some other coronaviruses. MERS has 2 of them. infectious bronchitis virus (IBV) Beaudette strain, a chicken coronavirus, has 2. People have presented a credible origin of the furin cleavage site by a simple copy-choice mistake by the viral polymerase.

Response: This is again essentially the same comment made by reviewer 3. Reviewer 4 here even "cited" the same words – "other viruses of this class" – as reviewer 3 did. However, as we have responded earlier, these words are nowhere to be found in our report. This is iron proof that at least one of the two reviewers had committed plagiarism.

We will not repeat our earlier response to this comment, except to point out that the reviewer ought to cite at least one reference to support his final claim. Without it, people have no way of judging how credible is the reviewer's theory that the furin-cleavage site could originate from a simple copy-choice error by the viral polymerase. Importantly, has such a copy-choice error led to the occurrence of a functional furin-cleavage site at the S1/S2 junction in any naturally occurring lineage B β coronaviruses? Also, what could be the molecular basis for having tandem CGG rare codons introduced here in SARS-CoV-2 *spike* by simple copy-choice mistake by the viral polymerase? We have provided extensive and in-depth analyses in our report to prove the non-natural origin of this furin-cleavage site. Having no answers to our questions

or showing no evidence when making unsupported claims like he did here dictates that the reviewer's argument is of no value.

Finally, her timing is odd. Why hasn't she published before. What will she submit soon? Why not now? I doubt anything substantive is coming.

Response: This again is the same comment made by reviewer 3. We have commented on the "issue" of timing in our response to reviewer 3 and will not repeat here again. In addition, contradictory to what this reviewer has predicted, we indeed have published a second report that substantiated our claim that certain coronaviruses have been fabricated to mislead the world on the origin of SARS-CoV-2[1]. This reviewer has been proven wrong once again.

It is shameful and utterly irresponsible that one of the two reviewers repeatedly copied from the other in a published peer review. Where is the independent, critical thinking? Is there any credibility in them giving advice to decision-makers on the issue of the COVID-19 pandemic?

Her research appears to be funded by the Rule of Law Society and the Rule of Law Foundation. The sister nonprofit organizations are connected to Steve Bannon, a former chief strategist for the Trump administration, and Guo Wengui, a billionaire and political activist who fled China in 2014 in anticipation of corruption charges from the Communist Party. Neither organization has published scientific literature before, according to a Google Scholar search. A website linked to Bannon and Wengui has a history of making inaccurate claims about the coronavirus pandemic.

Response: This again is the same exact issue raised by reviewer 3 earlier, which we have responded to previously.

Both reviewers crossed the line here as this issue has nothing to do with the science presented in our report. As peer reviewers, they are obligated to judge the article based on its scientific merits. The politicization by these reviewers on this topic is a shame.

Mr. Guo and Mr. Bannon did not know Dr. Yan until right before she escaped from Hong Kong at the end of April 2020. By then, Dr. Yan had been anonymously exposing various facts of the COVID-19 pandemic for over three months, and all the information she shared had been verified.

~~Mr. Guo started exposing the corruptions and injustice of the CCP regime since 2017. His efforts have led to the awakening of many Chinese people and have encouraged them to pursue freedom, human rights, and equality. Because of these actions, Mr. Guo has been brutally attacked and defamed by the CCP regime. The *Rule of Law Foundation* and *Rule of Law Society* were founded by him, which played a pivotal role in assisting Dr. Yan's escape from Hong Kong so that she could now tell the truth of COVID-19 to the world.~~

(*Comments on July 17th, 2021*: Because the ROLF & ROLS unilaterally requested to have our reports closed, which violated the rules of scientific publications, we have changed our affiliation in responding to this situation. Relevant contents in the above paragraph were crossed out because we believe our earlier views on this matter were misled and such descriptions do not truthfully reflect real events. Similarly, concerning Guo, due to the recent developments, we felt necessary to remove the relevant descriptions.)

Finally, given the reviewer's severe incompetency in understanding the coronavirus biology as evidenced in his comments, it is clear that he has no authority in judging what are accurate claims or what are inaccurate claims about the coronavirus pandemic. He has proven himself simply not credible.

To more specifically review Yan's publication, let's look at her **Abstract**.

1. She says the natural origin theory lacks substantial support. No it doesn't(*1-3*). This seems deliberately deceptive.
2. She says papers claiming a man-made origin are strictly censored by peer reviewed journals. As a sometime peer reviewer, I don't call peer review censorship.
3. She says the virus shows biological characteristics that are inconsistent with a naturally occurring, zoonotic virus. Dubious claim.
4. She postulates a synthetic route that is partly doable but tedious, and is otherwise logically impossible.

Response:

1. Reference 1 listed by the reviewer[15] was promoting the natural origin theory and yet the arguments within were founded upon RaTG13 and pangolin coronaviruses. With RaTG13 and pangolin coronaviruses proven fraudulent[1], this reference is now proven of no value. Reference 2 and 3 do not support the natural origin theory[35,36]. Rather reference 3 proved that genetic engineering of the Spike could turn a bat coronavirus into a novel, artificial coronavirus that is capable of using human ACE2 for cell entry and infection[35]. In fact, here, the reviewer used a reference that supports, not dismisses, our first report. This indicates that the reviewer is either unfamiliar with the relevant literature in coronavirus research or is careless in giving his reviewer's comments.

2. The censorship on the lab origin theories by journals has been documented in an article[27], which we have cited in our report (reference #22)[5]. Furthermore, email exchanges between signees of the *Lancet* statement, which were exposed by the *US Right to Know*[37-39], clearly indicated that the journal *Lancet* was promoting the natural origin theory without supporting evidence and at the same time called the lab origin claims "conspiracy theories" also without putting forward any evidence.

   The reviewer argued that his own experiences do not suggest peer review censorship. We would argue that his actions here indeed provided a fine example of peer review censorship on this sensitive topic. Having functioned in the role of a peer reviewer does not mean that one is a competent or qualified peer reviewer. This reviewer's comments and behavior here showed convincingly that he is completely incompetent and unqualified as a reviewer. Yet, he was placed in the role of a "reviewer" regardless. If our report had to be approved by a peer reviewer like him to be published, then it simply would not get published despite that it is solid scientifically.

3. Part 1 of our report, which is at least half of our overall content, was dedicated to supporting and proving just this claim. Compared to the substantial evidence and analyses we have provided in part I of our report[5], the two-word comment, "dubious claim", of the reviewer weighs next to zero scientifically.

4. Similarly, the reviewer came to his conclusion about our postulated synthetic route without providing any reasoning or literature support. While the route postulated by us is convenient, inexpensive, verifiable, involving established techniques and available materials, and still popular in top labs doing coronavirus research, the reviewer failed to propose anything realistic himself. His comment is, once again, invalid.

The **Introduction**

1. She says it has characteristics that are incompatible with a zoonotic respiratory virus, including being highly transmissible and significantly lethal in high-risk populations. The Incas would be relieved to know that measles, derived from rinderpest in cattle, does not share those characteristics.
2. She claims that the receptor binding domain of the spike protein binds human ACE2 better than any other species. No it doesn't; it binds various ACE2 receptors from other species about as well, including pikas and rabbits https://onlinelibrary.wiley.com/doi/full/10.1002/jmv.25817 . Her citation is a non-peer reviewed in silico modeling study.
3. She accuses the reports of the sequence of one of the purported precursors to SARS2, RaTG13, as being probably fraudulent. The references she gives are either weak or don't claim this at all. In fact, one of them notes that six workers in a cave from which a closely related sample was obtained from bat feces suffered from an atypical viral pneumonia and three of them died in 2013 (https://www.preprints.org/manuscript/202005.0322/v2). This would rather seem to point to the reality of RaTG13.

Response:

1. Our exact description was "*(a)s a coronavirus, SARS-CoV-2 differs significantly from other respiratory and/or zoonotic viruses: it attacks multiple organs; it is capable of undergoing a long period of asymptomatic infection; it is highly transmissible and significantly lethal in high-risk populations; it is well-adapted to humans since the very start of its emergence1; it is highly efficient in binding the human ACE2 receptor (hACE2), the affinity of which is greater than that associated with the ACE2 of any other potential host*". Apparently, we did not suggest that any single feature listed is unique for SARS-CoV-2. Instead, we meant that these features collectively make SARS-CoV-2 unique among respiratory and/or zoonotic viruses. The reviewer manipulated our description and took things out of context in making his comment and criticism. Were measles well adapted to humans at the very beginning? Did the initial measles strain, which just crossed over into humans, bind human receptor optimally over the receptor of any other animal? Furthermore, our conclusion on the laboratory origin of SARS-CoV-2 was also based heavily on the genetic evidence, such as the "smoking gun" that matches the cloning routine of Drs. Zhengli Shi and Fang Li[7,28], suggesting past genetic manipulation of the genome. Could the reviewer point to similar marks of genetic manipulation in measles to prove his point that all characteristics of SARS-CoV-2 are precedented? Clearly, our original statement is accurate and appropriate. The reviewer's counterargument here, however, is invalid.

2. We had cited two publications when we made this point in our report. However, the reviewer picked only one and questioned the validity of this citation since it is a *in silico* study[40]. The reviewer intentionally left the other citation out, which looked at the RBD-ACE2 binding using a robust biochemical assay[41]. The results of both studies prove that the SARS-CoV-2 RBD binds human ACE2 the best. What ridicules the matter further was that the article that the reviewer used as a counterargument here is also an *in silico* study and did not even describe binding energies for the pairs of RBD-ACE2 that they modeled. This comment speaks in volumes of the reviewer's incompetency as a peer reviewer and a scientist in general.

3. The references we provided in regarding to RaTG13 were robust and consistent with our description. More importantly, we have published our second report, which has proved RaTG13 fraudulent[1]. We also have offered our insights to reject the Mojiang Miner Passage hypothesis (section 1.6 of our second report). RaTG13 is a fabricated virus, not obtained from a cave or any other place in nature, and Mojiang cave is not the home of SARS-CoV-2.

The Proposed Construction

It is necessary for her to claim that a number of sequences (including RaTG13, 97% identical by nucleotide sequence) are fraudulent, because its absence allows her to use ZC45 (89% identical by nucleotide sequence). She probably chose this because she could link it to the military. Here's what she suggests. She says you start with ZC45 as a precursor. At 89% identity, you would need about 3,300 nucleotide changes. You engineer in an ACE2 receptor binding domain and furin cleavage sites. OK, although that ACE2 binding site is not optimal for ACE2 binding. Then you engineer in a pol gene that responds well to remdesivir (because this gives you a good antiviral and would make remdesivir profitable). Then you adapt the virus by passage in culture for the ability to better infect human cells. This step, however, is simply beyond belief. You would need more than 3,000 individual mutations. This probably represents hundreds of millenia of evolution. It's even more incredible because coronaviruses have RNA proofreading enzymes that make them fairly stable genetically, although they do readily undergo recombination by RNA polymerase template slippage or switching.

Response: The reviewer is completely mistaken here.

First, these mentioned coronaviruses, RaTG13, a series of pangolin coronaviruses, RmYN02, are indeed fraudulent. We have provided substantial evidence in our second report in proving so[1]. If the reviewer disagrees with our second report, he needs to come up with robust, evidence-based scientific arguments, not empty comments, to contest our analyses and conclusions.

Second, we have provided evidence on why ZC45/ZXC21 must be the template/backbone used for the creation of SARS-CoV-2, part of which is the 100% sequence identity on the E protein between SARS-CoV-2 and ZC45/ZXC21. Before the publication of RaTG13, ZC45 and ZXC21 were the closest match genetically to SARS-CoV-2, which we have elaborated in our response to review 1.

Third, the reviewer is also awfully mistaken in stating that SARS-CoV-2 Spike is not optimized for binding human ACE2. The literature evidence all speaks overwhelmingly against his statement – it has been shown repeatedly and consistently that SARS-CoV-2 RBD binds the human ACE2 better than to ACE2 of any other animal[40-43]. The reviewer's lack of knowledge on this subject proves once again that he is severely and dangerously underqualified as a peer reviewer here.

Fourth, we have never stated that the chosen RdRp would respond well to remdesivir. Instead, we listed two possible reasons why the CCP scientists would want to incorporate a particular RdRp gene into the artificial genome of SARS-CoV-2. One of the possible reasons was that they may see this particular RdRp more amenable toward antiviral drug discovery. This review comment, written by reviewer 3 or reviewer 4 and copied by the other, made it evident that these two reviewers were unable to read and understand a well-written scientific report. They, once again, failed to meet the standard of competent peer reviewers here.

Fifth, the reviewer was wrong in assuming that changes as many as 3,000 could not be introduced into the genome of a template coronavirus when artificially creating a novel coronavirus. We have explained this issue in our response to review 1 and will not repeat those details here again. However, one thing we do want to point out is that, as we have described both in the original report and in responding to review 1, most of these changes should have been introduced at steps prior to serial passage. Although the serial passage step may introduce some changes, it is not where majority of nucleotide mutations were introduced. Therefore, the reviewer's arguments that "*(t)his probably represents hundreds of millenia of evolution*" and "*coronaviruses have RNA proofreading enzymes that make them fairly stable genetically*"

are simply irrelevant; they do not support his argument that significant changes could not be introduced. He again failed, shamefully, to understand our report.

My opinion is that this is an inept attempt to make the case the virus was man-made. There are no concrete facts in this report. I do wonder why this is coming out now. She implies she will be coming out with something more convincing in the future, but I'm willing to bet that if anything comes it will just be more of the same.

Response: **Unfortunately, most of Dr. Reitz's comments are completely incorrect and the rest of them are opinions that lack scientific support entirely. The only thing he succeeded here was to prove to the world that he is not credible as a reviewer, which dictates that his conclusion about our report is of no value.**

If Dr. Reitz or any of the other reviewers truly believe their argument that SARS-CoV-2 must have come from nature, we suggest that they, working either individually or together, write formal, evidence-based article(s) to support this view of theirs. We would consider commenting on it, although, judging from the quality of their "review" comments here, we are very much convinced that their article(s) on this topic would be of very low quality scientifically.

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Part II:

Point-to-Point Responses to

"Reviewers" from Johns Hopkins Center for Health Security

On Sep 21st, Kelsey Lane Warmbrod, MS, MPH; Rachel M. West, PhD; Nancy D. Connell, PhD; and Gigi Kwik Gronvall, PhD; all from the Johns Hopkins Center for Health Security published a "peer review" commenting on our scientific report "*Unusual Features of the SARS-CoV-2 Genome Suggesting Sophisticated Laboratory Modification Rather Than Natural Evolution and Delineation of Its Probable Synthetic Route*"[1]. Their writing can be found on their website[2]. While peer review is a mechanism to ensure the robustness of a scientific publication, it is to be provided by scientists with matching expertise. However, unfortunately, the comments offered by Warmbrod et al. showed clearly that these self-claimed "reviewers" do not have adequate knowledge in any of the relevant areas of biology, including virology, molecular biology, evolutionary biology, structural biology, and biochemistry. A closer look at the background of the "reviewers" showed that, indeed, none of the four scientists has worked on coronavirus or on any aspect of virology. More importantly, Warmbrod et al. repeatedly distorted our descriptions in their comments and then inserted their otherwise unjustified criticisms. Their intention to mislead the public and muddle the water on the true origin of SARS-CoV-2 could not be more evident. Dr. Yan and her co-authors always welcome evidence-based, logical, and honest scientific discussions on the Yan reports. However, we condemn pretentious and dishonest "peer reviews" of our reports. We believe that the significant amount of incorrect information provided in Warmbrod et al.'s criticisms pose threat to the world's understanding of the origin of SARS-CoV-2. Therefore, here we provide point-to-point responses to their criticisms, which we hope would provide clarity to issues muddled by Warmbrod et al. and help the scientific community and the general public better understand our original report and the true origin of SARS-CoV-2.

Point-to-Point Responses

Page 2

1. **On natural existence of a closely related virus.** Line 17: RaTG13 is a previously discovered bat coronavirus which has about a 96% sequence identity to SARS-CoV-2,[4] indicating that it is a close relative and that bats are likely involved in the evolution of SARS-CoV-2. Yan et al question the existence of RaTG13, which is found in GenBank.[11] The authors cite multiple papers in their reference section that have weaknesses or flaws to make their case. In their paper, reference 7's author is not a scientist or researcher according to his ORCID profile; references 10 and 13 cannot be found online and the links provided are not active; reference 11 is an opinion piece on an anti-GMO interest group website; references 5, 6, 8, 9, and 12 appear to be authored by scientists lacking expertise in coronaviruses and/or viral evolution. Only 2 of these publications (14 and 15) were published in scientific journals with peer review, and none of the authors of these 2 articles specialize in coronaviruses or viral genetics.

Response: Contrary to the reviewers' claim, references 5, 6, 8, 9 and 12 were produced by scientists, whom all have backgrounds related to infectious disease and/or virology. In contrast, Warmbrod et al. have no background in virology at all.

The original link for our reference 13 is indeed broken. In fact, it only became broken after our report was published. The author of reference 13 had reposted his article here[3], where he also posted a note explaining how the link to his article had become broken right after our report was published:

"*Author's Note - This is a reposting of the original article posted on LinkedIn on April 2, 2020. Something strange happened in September. The link to my original article was severed sometime two days after Dr. Li-Meng Yan's paper was published on Sep. 14, 2020. Dr. Yan's paper, unbeknownst to me, quoted my original article as Reference #13. A LinkedIn connection of mine informed me of the severed link on Sep. 19, 2020. Another LinkedIn connection confirmed on the same day the severed access to my original article and noted that he could access the article two days after publication of Dr. Yan's paper, on Sep. 16. So later on Sep. 19, I sent a message to LinkedIn CEO, Mr. Ryan Roslansky, inquiring about the reason for the severance. LinkedIn's Customer Support later replied that "a bug is preventing us from releasing the article to the site" and asked me to repost the article. So here it is."*[3]

Warmbrod et al. were also mistaken on reference 10. The online link of this reference is valid. Reference 11 is an opinion piece, however, the scientists who offered opinions within this report were clearly experts in their respective fields.

We do not know whether the author of reference 7 is a scientist or not[4]. The scientific merits and critical thinking of this reference are significant, which is the criteria that we followed for selecting our references. It was nothing but appropriate for us to cite this article in our report.

Importantly, contrary to the reviewer's claim, RaTG13 is a fabricated virus. We have provided substantial scientific evidence in the final paragraph of section 1.1 in our report, which showed that the existence of RaTG13 in nature is questionable. **More importantly, we have published our second report[5], which presented overwhelming evidence and analyses proving the fraudulent nature of RaTG13.** To possibly dismiss our conclusion here, the reviewers have to come up with a valid, evidence-based counter-argument to prove the validity of RaTG13.

2. **On the capacity to predict function from genotype.** Line 28: Yan et al overstate the capabilities of deducing functional changes from genetic manipulation of coronaviruses, referring to an "abundant literature indicat[ing] that gain-of-function research has long advanced to the stage where viral genomes can be precisely engineered and manipulated to enable the creation of novel coronaviruses possessing unique properties."[10] Technologies like CRISPR have enabled precise, directed gene editing, and are major advances for the biological sciences. However, the report overstates current capabilities in designing phenotypes and genetic functions of viruses, which are not already elucidated, including coronaviruses, and vastly overstates the capabilities of genetic manipulation of coronaviruses in 2019, before these viruses were the focus of worldwide interrogation by the scientific community. There were 6 coronaviruses known to infect humans prior to 2020, but their prevalence and pathology in different age groups is incompletely understood, which would hamper any potential design of novel coronavirus functions. Prior to 2020, coronaviruses were not as intensely researched as other viruses that cause human disease, such as HIV, and influenza.

Response: Warmbrod et al. are mistaken in stating that there is lack of capabilities in gain-of-function research in coronaviruses. Instead, genetic manipulation of coronaviruses have been done extensively as evidenced by the literature[6-15]. Gain-of-function research where certain genes are engineered and manipulated in a specific manner has led to novel coronaviruses capable of using the human ACE2 receptor for infections[6,7,10,16]. The corresponding description in our report was a fair statement of the current capabilities, not an overstatement. Dr. Ralph Baric, who is the top expert in constructing synthetic coronaviruses, stated in September 2020 that "*you can engineer a virus without leaving any trace*"[17].

Warmbrod et al. clearly lack the knowledge in the status and development of coronavirus research in the past two decades.

Furthermore, coronavirus research is especially extensive and proliferic in China. Since the SARS epidemic in 2003, the coronavirus research in China has enjoyed a two decades-long, sustained support from the CCP government. As a result, labs under the control of the CCP have the largest collecitons of coronaviruses (both sequences and physical samples) as well as ample experience in gain-of-function research in this area.

Finally, the fact that all past coronaviruses were only modestly prevalent and SARS-CoV-2 caused a world-wide pandemic uniquely speaks for, not against, the suspicious nature of SARS-CoV-2. Natural occuring coronaviruses have never led to this scale of a pandemic or caused this many deaths worldwide.

3. **Lack of current evidence countering natural origin theory.** Line 27: Yan et al refer to an extensive scientific literature providing "genomic, structural, and literature evidence"[10] to counter the prevailing theory in the scientific community that the origin of SARS-CoV-2 is a natural zoonosis, emerging from animals, but they do not cite any references to support their claim—a crucial basic practice for any researcher.

Response: Apparently, Warmbrod et al. failed to understand that our whole report was dedicated to provide such genomic, structural, and literature evidence to prove that SARS-CoV-2 is an unnatural virus. If Warmbrod et al. keep on reading from this line 27, later in the same paragraph they would have found our statement that "*(i)n this report, we present such evidence and the associated analyses.*" Consistent with this statement, genetic, structural, and literature evidence was described, analyzed and discussed in great details throughout our report. The inability of Warmbrod et al. to recognize this is astonishing. It shows that they are either very poor in their quality as scientists or intentionally misleading in writing this comment.

Page 3

1. **On implausibility of the proposed viral genetic backbone.** Lines 19-20: Scientific evidence suggests that many coronaviruses[12] similar to SARS-CoV-2 have a recent common ancestor or that convergent evolution[13] has occurred. Many coronaviruses infect bats and other animals, most of which have not been analyzed, so the evolutionary record has gaps until more samples are collected. Convergent evolution[14] refers to the evolution of similar traits in independent organisms. Yan et al do not attempt to refute the prevailing scientific evidence on viral evolution, but assert that ZC45, a coronavirus with over 3,000 punctuated, broadly distributed nucleotide differences from SARS-CoV-2 (a significantly large number of differences), could have been used as a "backbone" or template to produce SARS-CoV-2 synthetically. ZC45 is a beta coronavirus[15] isolated from a bat between 2015 and 2017 in Zhoushan city, Zhejiang province, China. ZC45 and ZXC21 were both discovered and characterized in to better understand animal reservoirs of SARS-like coronaviruses. No explanation is given for how the over 3,000 nucleotide differences SARS-CoV-2 and ZC45 could be produced; this process would be highly challenging for deliberate engineering.

Response: Our report did not deny that β coronaviruses exist and evolve in nature. Our assertion on the use of ZC45/ZXC21 as the template for the creation of SARS-CoV-2 was based on various genetic evidence, including the 100% identity on the E protein between SARS-CoV-2 and ZC45/ZXC21, as well as the fact that a fabricated RaTG13 virus was used to specifically make people overlook the connection between ZC45/ZXC21 and SARS-CoV-2.

However, although SARS-CoV-2 was created based on ZC45/ZXC21, during its creation, changes must have been introduced to obscure the genetic connection between the two. In addition, some random mutations must have also accumulated when the assembled, live virus was developed in subsequent experiments, which should have further contributed to the overall genetic divergence between SARS-CoV-2 and ZC45/ZXC21. If no changes were introduced, the weaponized virus could be immediately traced back to its backbone, revealing the true identity of not only this novel viral pathogen but also the scientists involved in its creation.

In our report, we have delineated how sequence differences could be introduced (section 2.2 and Figure 7) during the creation of SARS-CoV-2 using ZC45/ZXC21 as a template. For the Spike protein, in addition to the modified RBM, the rest of the sequence would have changes introduced at the initial step, which is DNA synthesis. The Orf1b gene should have been taken from another SARS-like coronavirus, RaBtCoV/4991, which would differ naturally from ZC45/ZXC21. Two likely reasons for the use of this specific Orf1b have been described in section 2.1 of our report[1]. The rest of the genome also could be obtained through DNA synthesis, where changes can be easily introduced.

Here, the introduced changes are of two types. First, they could introduce synonymous mutations. Although ZC45/ZXC21 and SARS-CoV-2 are 89% identical to each other on the nucleotide level, they are 95% identical on the amino acid level. Clearly, over half of the nucleotide differences are synonymous mutations, which does not alter protein structure or functions. In fact, as shown in the literature, codon-optimization had been done successfully for Spike[6], which entails that synonymous mutations can be safely introduced into the *spike* gene. The same could be easily applied to other sections of the genome. Second, amino acid changes could be introduced into variable regions/positions of a protein without affecting its structure or function. This could be safely guided by multi-sequence alignment of the many SARS and SARS-like virus sequences, which the WIV has in great abundance. The process of introducing changes, both synonymous mutations and amino acid substitutions, into a template virus has been nicely illustrated in a 2008 publication (Figure S1 of this article)[10].

Finally, we do not rule out the possibility that some changes in the SARS-CoV-2 genome could have been introduced to enable novel functions. It remains to be revealed whether certain complications associated with COVID-19, some of which are rare or non-existent in other coronavirus infections, are results of intentional design. This speaks to the necessity of treating SARS-CoV-2 for what it really is. Without acknowledging its true nature as a bioweapon and obtaining all the details of its creation, the world may continue to be misled to overlook key aspects of this pathogen and thereby suffer severely from it for a long period of time.

2. **Role of Chinese military lab.** Lines 4-6: The United States has a number of high-containment laboratories in which viruses can be studied safely with engineering controls, including negative air pressure. Some of these labs are located at military laboratories, such as the US Army Medical Research Institute of Infectious Diseases in Frederick, Maryland. China, France, Germany, India, Russia, the United Kingdom, and many other countries similarly have laboratories operated by military researchers that are declared to the Biological Weapons Convention in confidence-building measures. Scientific investigation in military laboratories is not uncommon; coronavirus research performed in a Chinese military research institute is not in itself suspicious, as asserted by Yan et al.

Response: Warmbrod et al. once again distorted the meaning of our report. Our exact words here were:

"*The genomic sequence of SARS-CoV-2 is suspiciously similar to that of a bat coronavirus discovered by military laboratories in the Third Military Medical University (Chongqing, China) and the Research Institute for Medicine of Nanjing Command (Nanjing, China)".*

Clearly, what we have referred to as suspicious was the sequence similarity between SARS-CoV-2 and ZC45/ZXC21. Not at all should our writing be interpreted as all scientific investigations in military laboratories are suspicious. Like in other places, Warmbrod et al. intentionally distorted our meaning to create room, which is otherwise non-existent, to insert their criticisms.

With that said, we do believe that the CCP military played a role both in the creation of SARS-CoV-2 and in the cover-up after it is unleashed into the human population. As shown in our second report[5], the fabrications of pangolin coronaviruses involved the *Academy of Military Medical Sciences* (AMMS) in multiple accounts[18-21]. These fabrications were used as cover-ups to mislead the world into believing that SARS-CoV-2 has a natural origin. The extensive cover-up involving Chinese military research groups is extremely evident. Could Warmbrod et al. offer examples of large-scale, government-organized fabrications of viruses that were used to cover up the origin of SARS-CoV-2 or any other viral pathogen? Or could Warmbrod et al. provide evidence to prove that the pangolin coronaviruses published by the Chinese military research groups are not fraudulent? Without these, they have no basis to deny the involvement of the CCP military scientists in the creation and cover-up of SARS-CoV-2.

3. **Furin cleavage sites in coronaviruses.** Lines 10-16: The authors assert that a furin cleavage site in its Spike protein is absent in coronaviruses found in nature, which is not the case. SARS-CoV-1 and Middle East respiratory syndrome (MERS) have furin cleavage sites in their Spike protein. This is fairly common in other coronaviruses[16]; MERS has a furin cleavage site[17] within Spike.

Response: Warmbrod once again distorted our report here to then launch their otherwise unjustified criticism. We have clearly stated that, except for SARS-CoV-2, no lineage B β coronaviruses have furin-cleavage site at the S1/S2 junction. Yet, Warmbrod et al. distorted our description and omitted "lineage B β" and "at the S1/S2 junction" here in their criticisms. Such intentional distortion of our report has shown up repeatedly in their comments, which not only proves the biased nature of their review but also put their motives in question.

Furthermore, SARS-CoV-1 does not have a furin-cleavage site at the S1/S2 region. It has a furin-cleavage sites at the S2'. For MERS, there is a furin-cleavage site at the S1/S2 junction. However, MERS does not belong to the lineage B of β coronaviruses. Therefore, our original description – *"(w)ithin the lineage B of β coronaviruses and with the exception of SARS-CoV-2, no viruses contain a furin-cleavage site at the S1/S2 junction*"[1] – was accurate and factual.

4. **Dissimilarities between SARS-CoV-2 and ZC45.** Figure 1.1: The report features a figure comparing sequences of various coronavirus strains. The figure's data appear accurate and demonstrate a high degree of dissimilarity between ZC45 and SARS-CoV-2, particularly in ORF1a, but the conclusion made by the authors in the text is that the strains are similar. Neither the figure nor the text clarify which genome serves as the reference.

Response: Warmbrod et al. used this same trick here again to fool its readers – they distort our true description. Our exact description here on the similarity between ZC45 and SARS-CoV-2 was:

"*Searching the NCBI sequence database reveals that, among all known coronaviruses, there were two related bat coronaviruses, ZC45 and ZXC21, that share the highest sequence identity with SARS-CoV-2 (each bat coronavirus is ~89% identical to SARS-CoV-2 on the nucleotide level)*"

Our description here is true and accurate. We clearly did not try to characterize this level of sequence identity as similar or dissimilar. However, Warmbrod et al. incorrectly described our writing.

We did describe ZC45 and ZXC21 as similar when we talked about Figure 1:

"*ZXC21, which is 97% identical to and shares a very similar profile with ZC45, is not shown*"

Clearly, Warmbrod et al. stitched two separate, unrelated descriptions of ours into one sentence and thereby fabricated a statement that we did not actually make.

Finally, in the legend of Figure 1, we clearly stated that "*similarity plot based on the full-length genome of 2019-nCoV WIV04*". Anyone with a brain can understand that the genome of 2019-nCoV WIV04 was used as the reference genome here in Figure 1. However, Warmbrod et al., once again, wrongfully accused us of not clarifying what the reference genome was. To say that they acted with a strong bias is clearly a severe understatement of the situation here.

Page4

1. **Similarity of ORF8 between SARS-CoV-2 and ZC45.** Lines 9-14. The authors' assertion that the similarity between the ORF8 gene in SARS-CoV-2 and ZC45 is unnatural (relative to sequence conservation among coronaviruses) is not supported by evidence presented. While the sequence of ORF8 varies among coronaviruses, its function is not well characterized.[18] In line 10, the authors report that ORF8 may be involved in SARS-CoV-2's ability to evade the host immune response (and thus affect pathogenicity). They then suggest that ORF8 is usually dissimilar among different coronavirus strains, based on a paper by Muth et al[19] that studied deletions in ORF8 during the 2003 SARS-CoV-1 epidemic. Muth et al found that a deletion of 29 nucleotides in ORF8 of SARS-CoV-1 attenuated the virus by decreasing the virus's ability to replicate. A recent paper[20] identified the role of ORF8 in pathogenesis of SARS-CoV-2 as potentially playing a role in viral maturation and assembly. Importantly, this study on ORF8 was published *after* the emergence of SARS-CoV-2, whose mode of action is still not fully understood; this timeline does not align with Yan and colleagues' proposed timeline of events. Furthermore, the authors fail to consider the level of similarity in ORF8 between viral variants of the same strain, which could provide better context for the sequence identity between different strains. It is, therefore, inappropriate to suggest that the similarity of SARS-CoV-2 and ZC45 is unusual.

Response: Warmbrod et al. once again distorted our descriptions. We have described the high sequence identity (94%) on Orf8 between SARS-CoV-2 and ZC45/ZXC21 as "unusual". However, at the beginning of the comment above, Warmbrod et al. replaced our word "unusual' with the word "unnatural", which distorted the meaning of our analysis. The rest of Warmbrod et al.'s comments here are irrelevant. We never said that the function of Orf8 is suggestive of the origin of SARS-CoV-2. Warmbrod et al. literally did not understand our report and made a comment that was neither relevant nor coherent.

Our point in the report was clear: the 94% sequence identity on Orf8 between SARS-CoV-2 and ZC45/ZXC21 is unusual when no more than 58% sequence identity is exhibited between SARS-CoV-2 and any other naturally occurring coronavirus on Orf8. We continue to stand by this statement.

2. Also, lines 11-13: ZC45 and ZXC21 seem to have an 94% identity with ORF8, which is greater than with other circulating coronaviruses (59%), but this is still quite low. ORF8 has been identified[20] as a protein of interest in aiding in virus assembly/packaging. Yan et al argue that SARS-CoV-2 is suspiciously similar to SARS-CoV-1, yet these 2 viruses contain less than 20% similarity in their ORF8 sequences.

Response: We have never said that SARS-CoV-2 is suspiciously similar to SARS-CoV-1 on anything other than the RBM. Here, Warmbrod et al. intentionally carved our words out of our discussion on the RBM, and falsely claimed that these words were used for our description of the overall

similarity between SARS-CoV-1 and SARS-CoV-2. Such manipulations by Warmbrod et al. distorted our report severely. Their behavior here is simply despicable.

Page 5

1. **Mischaracterization of sequence homology data.** Lines 9-10, referring to Figure 2: The authors present a variety of homology data that are superfluous, internally inconsistent, or misinterpreted in the text. For example, the authors state that the E protein, which plays a minimal role in pathogenesis, is highly variable; however, the Figure 2 shows a fairly stable amino acid sequence. In lines 4-5, the authors state that SARS-CoV-2's E gene is highly permissible to mutations because in a 2-month period there have been 4 nonsynonymous mutations. They use this to suggest it is suspicious that early SARS-CoV-2 samples had identical identity to the purported "backbone" viruses, when SARS-CoV-2 is able to tolerate nonsynonymous mutations to the E gene and, therefore, it would be unlikely for SARS-CoV-2 to have evolved naturally to have 100% sequence identity. However, this analysis does not consider the selection bias in the samples' sequences and gaps in the existing phylogenetic trees. It is acknowledged in the field that there are gaps in the phylogenetic trees of the coronavirus family, making it difficult to determine accurately the likelihood of similarity between 2 viral variants. Additionally, Figure 2 shows only 1 sequence from an early time point in the pandemic and 4 samples from April. If other samples from February were to be included, then there might not be 100% amino acid sequence identity between SARS-CoV-2 samples and ZC45 and ZXC21. Finally, 2 strains of coronaviruses showing identical sequences in a particular gene could be an example of convergent evolution.[21]

Response: Warmbrod et al. once again distorted our description to make room for inserting criticisms. We have not described the E protein as highly variable or highly permissible to mutations. Instead, we stated that the E protein is tolerant and permissible to mutations even though it is a functionally conserved, structural protein.

Furthermore, Warmbrod et al. are shocking ignorant in phylogenetic analyses and evolutionary biology. The similarity is high when the sequence identity is 100%, which is true regardless whether there are gaps (missing species) in the phylogenetic tree. It is basic knowledge that sequence identities/homologies determine phylogenetic relationships, not vice versa. The lack of basic understanding of evolutionary biology here by Warmbrod et al. is astonishing.

Therefore, importantly, having possible gaps in the phylogenetic trees does not alter the fact that the 100% identity on the E protein between SARS-CoV-2 and ZC45/ZXC21 is highly suspicious.

Warmbrod et al. also argued that, if more samples from February were to be included, then there might not be 100% amino acid sequence identity between these SARS-CoV-2 samples and ZC45/ZXC21. Such a scenario, however, would further prove our point that the E protein is tolerant and permissible to mutations. An important fact here is that the earliest isolates of SARS-CoV-2 share 100% amino acid identities on the E protein with ZC45/ZXC21. Sequencing data clearly indicated that the selection pressure on the E protein is not strong or biased enough to purge away any amino acid mutations. The 100% identity on the E protein between ZC45/ZXC21 and the earliest SARS-CoV-2 isolates is highly suspicious.

Finally, Warmbrod et al. commented that convergent evolution could have led to the 100% identity on E between SARS-CoV-2 and ZC45/ZXC21. Although it is theoretically possible, in reality it is not. SARS-CoV-2 and ZC45/ZXC21 infect different hosts. Therefore, the cellular environment is significantly different for these viruses during their separate routes of evolution, which determines that the selection pressure is not going to drive the E protein into an identical sequence. The existence of an intermediate host would make it even more impossible. Rather, the opposite should be expected – no 100% amino acid

identity should be observed here. Again, the 100% identity on the E protein between SARS-CoV-2 and ZC45/ZXC21 is highly suspicious and a clear sign of ZC45/ZXC21 being used as the template for the creation of SARS-CoV-2.

2. **Binding with ACE2.** Lines 31-34: In a discussion about whether RaTG13 can bind various ACE2 homologs from different types of horseshoe bats, the authors neglect to point out that the ACE2 homolog of the specific species of horseshoe bat from which RaTG13 was isolated was not included in the cited binding studies. This makes conclusions about whether RaTG13 can bind ACE2 homologues incomplete.

Response: Warmbrod et al. once again altered the fact here. Our actual description was "*the receptor-binding domain (RBD) of the RaTG13's Spike protein could not bind ACE2 of two different types of horseshoe bats (they closely relate to the horseshoe bat R. affinis, RaTG13's alleged natural host)*". Clearly, we fully acknowledged that the ACE2 of *R. affinis* was not tested. Warmbrod et al. completely ignored this fact and criticized a "mistake" in our report, which we did not actually make.

3. **Binding of *Rhinolophus affinis* ACE 2.** Lines 34-36: Research[22] has shown that the receptor- binding domain of SARS-CoV-2 binds human, pangolin, and *Rhinolophus macrotis* bat ACE2 receptors optimally, and that the receptor-binding domain of *Rhinolophus affinis*, a type of horseshoe bat, did not bind the ACE2 of orthologous (different) horseshoe bat species' ACE2. *R affinis* ACE2 has not been well characterized, so it could not be tested. This is interesting work in progress but does not provide substantive conclusions about the provenance of SARS-CoV-2.

Response: This is an unbelievable comment, which shows that Warmbrod et al.'s knowledge of and understanding in coronavirus biology are extremely superficial.

Warmbrod et al. stated above that "*the receptor-binding domain of Rhinolophus affinis did not bind the ACE2 of orthologous (different) horseshoe bat species' ACE2.*" However, the RBD is not from *Rhinolophus affinis*, which is a species of bats. Rather, the RBD is from the RaTG13 virus, which was isolated from *Rhinolophus affinis*. The lack of knowledge by Warmbrod et al. is astonishing, which highlights the fact that Warmbrod et al. are completely unqualified in reviewing our report. In fact, their behaviors here – offering completely biased and mistaken reviews on a global health-related scientific report while totally unqualified in serving as reviewers – are unacceptable and reprehensible.

Natural evolution ensures that the ACE2 of *Rhinolophus affinis* would be much more homologous to ACE2 of closely related horseshoe bats than to human ACE2. When the ACE2 receptors from two closely related horseshoe bats do not bind RaTG13's RBD at all, it is not only safe but also reasonable to deduce that the ACE2 receptor from *R. affinis* may not be able to bind RaTG13's RBD. The inability to recognize, or knowingly denial of, this simple logic underscores the lack of qualifications of Warmbrod et al. as unbiased reviewers.

Page 6

1. **Missing methods section.** The report is missing a methods section, which is typically included in review articles[23] and allows for critical review of the process by which the articles reviewed were chosen. Information should be included about how the alignments were created, sequence quality, and adjustments for sampling bias—all factors that affect the results and conclusions.

Response: The comment is incorrect and misleading. Although we did not have a separate method section, we have provided sufficient details in figure legends to ensure that every single one of our analyses could be validated by others. Unlike what Warmbrod et al. have criticized, we indeed described how our

alignments were done. In the legend of Figure 2, we specified that "*alignments were done using the MultAlin webserver (http://multalin.toulouse.inra.fr/multalin/)*". We did not list this information again in Figure 4. However, it is the routine in a scientific paper that, when the same method was used for sequence alignment and the details of this method have already been provided in the paper, the same details do not have to be presented in full again.

All sequences used in our report are published on *GenBank*, and the quality of these sequences is ensured by the database. Our practice here does not differ from any published work. There is also no issue of sampling bias here. We specified clearly which sequences were used, and our conclusions, which are supported by our alignments using these sequences, remain valid under any combination of sequence sampling and alignment. To prove us wrong here, Warmbrod et al. ought to show which exact sequence is biased, why they could argue so, what an unbiased alignment would look like, and whether or not a different conclusion could be drawn here. They clearly did none of those here.

Importantly, Warmbrod et al. have no right to define what our report is. Our report is an evidence-based, strictly scientific publication, but not necessarily a review article. Nowhere in the world would they find a scientific review article that is complicated by all the following issues: it concerns a world-wide crisis; it is critical to global health and thus is extremely urgent; it has to deal with a series of large-scale, organized scientific fraud; it faces the resistance from a regime as powerful as the Chinese Communist Party.

In the end, the most important aspect of an article is its scientific quality and robustness, not the format or how the method information within is grouped. Consistent with this notion, in our report, we have presented substantial scientific data and analyses in a logical and coherent manner. We have also specified unique features of SARS-CoV-2 genome (restrictions sites, rare codons, evolutionary abnormalities, etc), which strongly support our conclusion that SARS-CoV-2 is of a lab origin. We also cited over one hundred references in a strictly scientific manner, which showed who had the necessary materials and information for the lab creation of SARS-CoV-2 and who has been engaged in relevant gain-of-function research.

Page 8

1. **On variability of Spike sequences.** Lines 1-13: There are various judgments about the similarity of SARS-CoV-2 sequences to other related viruses (ZC45 and ZXC21), but no inclusion of contrasting evidence. For example, S2 is not highly variable among coronaviruses,[24] but S1 is only a 69% match, making the claims that ZC45 was used as a template not credible. Convergent evolution, seen in several other viruses,[25,26] including SARS-CoV-1,[27] often as a virulence factor, should be considered by the authors.

Response: Warmbrod et al. once again showed their lack of quality as reviewers. If they had read the whole report and understood the contents at a basal level, they would have realized that, although ZC45/ZXC21 was used as a template, many changes must have been introduced into S1. Particularly, we have elaborated in great details how the RBM region of S1 was swapped. This manipulation would contribute significantly to a low sequence identity on S1 between ZC45/ZXC21 and SARS-CoV-2. Therefore, the low identity on S1 is not a piece of evidence against the notion that ZC45/ZXC21 was used as a template. Rather it strongly supports our overall conclusion that the lab creation of SARS-CoV-2 had involved genetic engineering and manipulation, not merely serial passages based on a naturally occurring coronavirus, such as ZC45/ZXC21.

We have detailed in section 1.2 of our report how convergent evolution could not lead to the natural occurrence of SARS-CoV-2. Apparently, it is not that we did not consider this aspect; it is Warmbrod et al. intentionally neglecting this part of our work in making their comment here. If any of our analyses

concerning convergent evolution is incorrect or questionable, Warmbrod et al. should specify it and offer their own analyses against it. A blunt ignorance and/or denial of our analyses is a behavior that is very inappropriate for reviewers.

2. **On substitution mutations within the Spike protein.** Lines 16-18: Substitution mutations that are hydrophobic and classified as minor in the report, are structurally significant and not minor; many mutations are lysines to phenylalanines, which alter structure, or phenylalanine to tyrosine which alter the charge of the side group.

Response: The comments here showed how shockingly ignorant Warmbrod et al. are in structural biology and biochemistry.

First, in our report, we pointed out that the hydrophobic substitutions specified would not alter the interaction between spike and ACE2. Recent data proved this to be the case: SARS-CoV-2 RBD binds to hACE2 exactly the same way as SARS RBD does[22]. Clearly, the reviewers' comment here has been proven wrong.

Second, Warmbrod et al. commented that many mutations are from lysines to phenylalanines. That is a ridiculous mistake. In our report, we have described these mutations as the following:

"*The few changes within the group of essential residues are almost exclusively hydrophobic 'substitutions' (I428→L, L443→F, F460→Y, L472→F, Y484→Q), which should not affect either protein folding or the hACE2-interaction.*"

The L443→F and L472→F mutations are what Warmbrod et al. were referring to here. However, they apparently do not possess the basic knowledge that "L" is the one-letter code for leucine, not lysine (one-letter code: K). Apparently, both mutations here are from leucine to phenylalanine, not from lysine to phenylalanine. It is simply unbelievable that Warmbrod et al. lack this very basic knowledge.

Finally, Warmbrod et al. described that mutation from phenylalanine to tyrosine would alter the charge of the residue. This is also plainly wrong. Neither of these two residues are charged. Warmbrod et al.'s level of knowledge in structural biology and biochemistry is embarrassingly low. They have once again proved that they are completely unqualified as reviewers for this report (and any other report involving structural biology or biochemistry).

3. **Quasiviruses and evolution of RNA viruses.** Lines 23-26: The authors make teleological assumptions in this passage. "As elaborated below, the way that SARS-CoV-2 RBM [receptor- binding motif] resembles SARS-CoV RBM and the overall sequence conservation pattern between SARS-CoV-2 and ZC45/ZXC21 are highly unusual. Collectively, this suggests that portions of the SARS-CoV-2 genome have not been derived from natural quasi-species viral particle evolution."[10] Currently, not enough is understood about SARS quasispecies[28] to argue definitively that a certain population arose from another or to eliminate the possibility of said evolution. Many of the Yan and colleagues' arguments could be explained by a mixture of convergent evolution, quasispecies, sampling bias, methodology issues, and/or a common ancestor.

Response: Warmbrod et al. are intentionally distorting the truth of our report with the goal of tricking their readers to believe that our theories are flawed.

In our actual report, what followed the above quoted writing of ours were detailed analyses showing how none of the possible evolutionary routes could produce SARS-CoV-2 through natural evolution. Our analyses considered all aspects mentioned here by Warmbrod et al., including convergent evolution, recombination, quasispecies evolution, selection pressure (sampling bias), common ancestor, etc. We specified in great details how each of the possible route is impossible and therefore dismissed.

By pulling together the words, Warmbrod et al. falsified a vague impression that natural evolution of SARS-CoV-2 is possible. However, not a single plausible evolutionary route for the natural occurrence of SARS-CoV-2 was provided by Warmbrod et al. that could explain the unusual features displayed in its genome. Their comment here is simply not a valid counter-argument against our analyses, which were detailed and fully elaborated.

4. **Viral recombination.** Lines 30, 31, and 43: The description of viral recombination does not accurately describe how this process occurs in viruses.[29,30] Viral recombination is a complex event,[31] which is not a "swapping" of entire genes, as the authors suggest, but a common, important part of viral evolution.[29] Reassortment can occur, but only in segmented, positive- sense RNA viruses. It is likely that ancestors of SARS-CoV-2 underwent viral recombination, though this is not necessarily a complete exchange of entire gene segments.

Response: Warmbrod et al. once again distorted our report in making this comment and criticism. The lines that Warmbrod et al. referred to here described how the RBM could be swapped in a recombination event. The RBM, which is the receptor-binding motif, is a not an "entire gene". Instead, it is a small segment of the *spike* gene. Clearly, we did not state that recombination leads to swapping of only entire genes. Warmbrod et al. described the situation incorrectly, which is inconsistent what was written in our report.

Also, it seems that Warmbrod et al. saw a word "complete" in our description and automatically assumed we meant complete/entire genes. In our actual writing, we described a virus with a "*relatively 'complete' RBM (in reference to SARS)*". Here complete RBM meant a RBM that does not have significant gaps comparing to the SARS RBM. The inadequacy of Warmbrod et al. as reviewers is, once again, astonishing.

Page 9

1. **The potential for zoonotic emergence of coronaviruses.** Line 9: There is not enough information available in the scientific literature to know whether strains related to SARS-CoV-2 may infect humans or if infections are possible but limited. Therefore, statements made by the authors about the infectivity of ZC45 are unsupported.

Response: Like many bat coronaviruses that have been studied before, ZC45 has large gaps in its RBM and is missing key residues that are indispensable for hACE2 interaction. Such viruses could not bind ACE2 to infect human cells[6,7,23-26]. The way to convert them into human cell-targeting viruses was through gain-of-function research, where either the Spike gene or just its RBM were swapped with the SARS RBM as demonstrated repeatedly by Zhengli Shi and colleagues[6,7,22].

Any competent scientist in the field would agree with our assessment that ZC45 "*would not be able to infect humans*". The inability to recognize so speaks for the lack of knowledge of Warmbrod et al. in the biology of coronaviruses.

2. **On intermediate hosts in viral evolution.** Lines 21-23: Viruses can have complicated evolutionary origins, sometimes with intermediate hosts,[32] as seen with influenza[33]; influenza viruses[34] are also known to crossover into humans. The human ACE2 (hACE2) receptor may be optimal for SARS-CoV-2, but recent work has found that SARS-CoV-2 can actually use multiple ACE2 receptors,[4] but not mice ACE2. More sampling needs to be done, but assertions about whether the hACE2 is the best receptor to bind SARS-CoV-2 cannot be supported at this time.

Response: Contrary to this comment of Warmbrod et al., all recent data showed that, although SARS-CoV-2 can bind ACE2 from different animals, hACE2 exhibits the highest affinity with SARS-CoV-2

Spike. This is supported by multiple publications and not opposed by any[27-30]. Warmbrod et al. are once again mistaken.

3. **Zoonotic emergence of coronaviruses in history.** Lines 36-38: Coronaviruses have caused human disease before, including SARS and MERS, and many have pointed to warning signs that coronaviruses could become a serious problem, which were not heeded prior to SARS-CoV-2. These facts are contradicted by the authors who also describe SARS-CoV-2 as "intelligent," which is teleological and counterfactual.

Response: Warmbrod et al. once again distorted our report in making this comment and criticism.

In our report, the word "intelligent" was not used to describe the SARS-CoV-2 virus, but rather used to describe the unusual way the SARS-CoV-2 RBM resembles the SARS RBM – having all key residues preserved and yet majority of the non-essential residues changed. Our exact words were:

"*Random mutations across the genome would have to have occurred to eventually shape the RBM to its current form – resembling SARS-CoV RBM in a highly intelligent manner.*"

It is the "design" that we describe as intelligent, not the virus. Our description here was accurate and factual, not counterfactual.

Furthermore, other coronaviruses causing human diseases in the past does not automatically dismiss the possibility that SARS-CoV-2 could be a product of gain-of-function work. The comment by Warmbrod et al. here lacks basic logic.

Page 10

1. **Lack of evidence regarding gain of function research in coronaviruses.** Line 2: Some gain of function research using coronaviruses has been published, but the author's statement of an "abundant" literature in this area overstates the amount known. The papers referenced do not support the author's claim that such research led to human competent viruses. One paper, Ren et al,[35] inserted the Spike protein gene of all SARS-CoV-like viruses (not SARS) into a viral backbone and did not use the entire SARS virus or infect live animals.

Response: The fact that we cited representative references here to prove our point does not negates our statement that the evidence on gain-of-function research is abundant. More such references had been provided in section 2.2 step 1 of our report[1]. The evidence undeniably proves that gain-of-function research on coronaviruses has been carried out repeatedly and the techniques involved are mature and well established. Ralph Baric also commented, based on his knowledge of the literature, that "*nowadays you could engineer a coronavirus without leaving any trace*"[17]. When the literature support is this fully and firmly, it is considered abundant.

Even though not all publications used SARS as the backbone and/or infected whole animals, all of these studies have produced novel coronaviruses that could infect human cells or cells carrying the human ACE2 receptor. The potential of these recombinant viruses to infect humans is nothing but evident.

2. **Lack of restriction sites in the proposed viral backbone ZC45.** Figure 5: The authors describe a possible pathway for designing viruses that is out of step with current scientific methods for gene editing, casting doubt on both their analysis and their conclusions. While use of restriction sites as presented are theoretically possible in SARS-CoV-2, based on the authors' own analysis, ZC45 does not have the necessary restriction sites (of EcoRI and BstEII). Therefore, ZC45 would have to be genetically modified beyond the sequence presented for a restriction digestion to be possible. This negates the authors'

argument that ZC45 is the obvious backbone of SARS-CoV-2. Restriction digests are not favored for manipulation of RNA viruses due to several obstacles: genome sizes, viral proofreading enzymes that can limit the success of restriction enzymes, and the ability to recover viruses after reverse genetic manipulation.

Response: The comments here by Warmbrod et al. are completely mistaken and full of error.

The genetic manipulation pathway we described is not out of step with current scientific methods. In fact, two top experts in coronavirus research, Fang Li and Ralph Baric, both published articles in 2020, respectively[22,31], where they used restriction digestion and ligation to generate their constructs of interests.

Also, their comment "*viral proofreading enzymes that can limit the success of restriction enzymes*" is so wrong that it is laughable. Here, they argued that the presence of proofreading mechanisms in a coronavirus would obstruct laboratory manipulation of the viral genome using restriction enzymes. However, proofreading enzyme functions *in vivo* when the virus is replicating in cells; it ensures that viral replication happens in a way that prevents the accumulation of a large number of mutations. Restriction digestion, however, is a method of genetic modification often used in gain-of-function research, which takes place *in vitro* before any *in vivo* experiments. In reality, it does not matter whether a coronavirus Spike is constructed by restriction digestion methods or not, and the viral genome replication would be safeguarded by the proofreading mechanism regardless. The comment by Warmbrod et al. here showed their complete ignorance in coronavirus biology, genetic engineering, and gain-of-function research. This group of "reviewers" is a complete disgrace to peer review and to the profession of scientists.

The need to introduce EcoRI and BstEII sites into ZC45 does not negates the possibility of ZC45 being used as the template for the creation of SARS-CoV-2. As we have described in our report, the introduction of these sites is extremely convenient and routine for trained molecular biologist. Furthermore, these two sites could even be introduced earlier through DNA synthesis of Spike, which requires even less time and effort in accomplishing. In fact, introducing restriction sites into *spike* through DNA synthesis had been done by Dr. Zhengli Shi in 2008[6]. There, Shi and colleagues synthesized codon-optimized *spike* gene. They subsequently used restriction enzyme digestion methods to swap the RBM. Although Shi and colleagues did not specify which restriction sites were used for the swap, it is no doubt that these sites were conveniently introduced through DNA synthesis[6]. Warmbrod et al. once again characterized the issue in a way that is inconsistent with the scientific truth.

Finally, we did not propose that genetic manipulation was done on a whole genome level. Instead, we clearly showed that the genetic manipulation of Spike should have been done separately in a cloning vector, which is the typical approach in the field[6,7]. Therefore, Warmbrod et al.'s claim that genome size could be an obstacle to genetic manipulation is, therefore, completely irrelevant to the pathway we proposed. It showed yet again that their understanding of the contents of our report was superficial and overwhelmingly mistaken.

Page11

1. **On restriction sites present within the Spike protein.** Lines 6-9: Restriction enzyme sites are found in all genomes and naturally occur frequently.[36,37] For instance, in a commonly used adenovirus vector, the BstEII restriction enzyme site occurs 10 times. The frequency of restriction site distribution is due to the fact that they comprise stretches of 6 or 8 consecutive nucleotides, which have high—and measurable—probabilities of occurring by chance within a given genome. With contemporary gene-editing methodologies, restriction sites are rarely used. These arguments aside, Yan and colleagues falsely assert the existence of restriction enzyme sites in the SARS-CoV-2 sequence, but not in the Spike gene sequence

of other beta coronaviruses, is evidence of genetic manipulation, or that the presence of restriction sites is rare. A New England BioLabs site search for restriction enzyme sites in the 5' end of the SARS-CoV-2 sequence revealed at least 7 other restriction sites in the RBM, in addition to the *Eco*RI site Yan et al cited as evidence of manipulation.

Response: Warmbrod et al. failed to acknowledge here that, in this comment of theirs, they left out the significant context that we described in our report.

In our report, we asserted that the existence of EcoRI and BstEII sites at either end of the RBM of SARS-CoV-2 was the "smoking gun" of genetic engineering. Importantly, this assertion was made in the context of the following key facts. First, EcoRI and BstEII at these two locations are unique only to SARS-CoV-2, but not to any other lineage B β coronavirus (excluding the fabricated coronaviruses published after the start of the outbreak). Second, the introduction of an EcoRI site breaks a conserved amino acid, Threonine (Thr). All naturally occurring lineage B β coronaviruses have Thr at this location. SARS-CoV-2 is the only one that carries a Serine (Ser) here, which is interlocked with having an EcoRI site here. Third, where EcoRI and BstEII sites are located matches exactly where Dr. Zhengli Shi and Dr. Fang Li (Shi's long-term collaborator and structural biology expert of Spike-ACE2 interactions) had cut and pasted RBMs using similar restriction enzyme digestion methods[6,22]. Fourth, we have reasoned in previous segments how the RBM of SARS-CoV-2 could not have been derived from natural evolution. Our assertion (the existence of EcoRI and BstEII sites at either end of the RBM of SARS-CoV-2 is the "smoking gun" of genetic engineering) was derived from considering all of these facts together. Apparently, Warmbrod et al. took our judgement out of its significant context, which was the opposite of being scientific. On the other hand, the fact that they could only "criticize" our analysis after taking things out of context proves the validity of our conclusion here. The genetic manipulation of RBM/Spike is undeniable.

Finally, the existence of contemporary gene-editing technologies does not mean that the genetic manipulation of the RBM here could not be accomplished by using restriction enzyme digestions. In fact, Dr. Fang Li swapped the RBM using restriction enzyme digestion methods in 2020[22]. Dr. Baric used restriction digestion in his recently published work too[31]. Clearly, for top experts, this old-fashioned technique was, as we have described, convenient and still the method of choice.

Page 13

1. The **possibility of convergent evolution in beta coronaviruses.** Lines 10-12: Yan et al state that there is only 1 evolutionary pathway that could explain the appearance of SARS-CoV-2—a homologous recombination event. However, convergent evolution is another pathway for the development of the furin cleavage site, which would result in SARS-CoV-2 having the cleavage site similar to nonbeta coronaviruses. Convergent evolution is a well-established phenomenon in biology.

Response: Warmbrod et al. are incorrect in making this statement. The difference between our analyses on this issue and Warmbrod et al.'s comment is that we analyzed the molecular basis of the evolutionary pathways, including convergent evolution, while Warmbrod et al. shared an opinion without any analysis or evidence.

In convergent evolution, different viruses might develop the same trait under certain evolutionary pressure. However, convergent evolution is the cumulative result of numerous evolutionary events, which at the molecular level are either random mutations or homologous recombination. Acquiring the furin-cleavage site requires 12 nucleotides being inserted at this junction region of the spike gene. Such an insertion could not be possibly achieved through random mutations. Therefore, we state that the only possible route for its natural occurrence would be recombination. We then offered our detailed analyses to show why recombination also could not be responsible for the emergence of furin-cleavage site at the

S1/2 junction of SARS-CoV-2 Spike. Clearly, our analyses took all possibilities, including convergent evolution, into consideration and dismissed all possible ways of natural occurrence of this particular furin-cleavage site in SARS-CoV-2.

In contrast, Warmbrod et al.'s comment lacked robust analysis on the molecular level. Their argument here is only an opinion that has no theoretical or literature support.

2. **The evolution of a furin cleavage site.** Lines 14-16: The authors argue that the existence of polybasic furin cleavage sites in other coronaviruses implies that convergent evolution could not have played a role in evolution of the furin cleavage site in SARS-CoV-2. The furin cleavage site refers to a specific position at the S1/S2 junction in SARS-CoV-2. This is a sequence of amino acids where the host (human) enzyme, furin,[38] can cleave. This furin cleavage is essential for the proper maturation[39] of the Spike glycoprotein and subsequent cell-to-cell membrane fusion in the host. They present the divergent furin cleavage site sequence in SARS-CoV-2 as evidence that homologous recombination between an ancestor beta coronavirus and a furin cleavage site-containing coronavirus is impossible. The argument that homologous recombination is not a likely factor in fact supports a hypothesis of convergent evolution.

Response: Here Warmbrod et al. argued for the same thing as they did in their previous comment. As we have explained in the above response, their argument is mistaken as there is no molecular basis for the convergent evolution to produce the furin-cleavage site naturally.

Convergent evolution not involving recombination, which is equivalent to evolution through random mutations only, would not result in an insertion of 12 nucleotides and thus the natural occurrence of the furin-cleavage site at the S1/S2 junction in SARS-CoV-2. Warmbrod et al's arguments here are baseless at the molecular level and clearly do not survive robust analyses.

It is also important to note that, in proposing their fatally flawed theory of convergent evolution, Warmbrod et al. clearly agreed with our analyses and conclusion that homologous recombination could not lead to the natural occurrence of the furin cleavage site at this location in SARS-CoV-2 Spike. These facts further prove that this furin cleavage site could not have come from nature.

3. **Homologous recombination.** Lines 18-19: The report states that the low sequence identity between beta coronavirus and other coronaviruses that contained a furin cleavage site would be too low to allow homologous recombination to occur. If recombination had occurred, it would not have had to have occurred in the immediate area of the sequence coding the furin cleavage site; it could occur in other, more homologous regions.

Response: Warmbrod et al. are mistaken here because the scenario described by them is an impossible one.

In our report, we have reasoned that, since no Spike protein that contains a furin-cleavage site is more than 40% identical to SARS-CoV-2 Spike, recombination could not be responsible for the natural emergence of the furin-cleavage site (FCS) at the S1/2 junction. Here, Warmbrod et al. indeed agreed with this analysis of ours, admitting that recombination could not have occurred within the *spike* gene.

They then implied that recombination could have happened in a way that a region greater than just the *spike* gene is swapped in from an FCS-containing coronavirus, through which the FCS within Spike is acquired. However, when such a swap takes place, because FCS-containing coronaviruses are highly divergent from the lineage B β coronaviruses that SARS-CoV-2 belongs to, the whole *spike* gene of SARS-CoV-2 must exhibit very low sequence similarity to the *spike* of other lineage B β coronaviruses while the rest of the SARS-CoV-2 genome share a much higher sequence similarity with other lineage B β coronaviruses. However, the reality is that the S2 of SARS-CoV-2 exhibits similar level of divergence

with other lineage B β coronaviruses as the rest of the genome does. Therefore, the scenario described by Warmbrod et al. is not possible. More importantly, it once again proves our point – this furin cleavage site could not have come from nature.

Consistent with the above notion, genetic evidence (tandem rare codons; FauI restriction site) also suggests that this FCS should have been inserted artificially[32]. In fact, introducing human protease-cleavage site into the Spike protein of coronaviruses to enable cross-species transmission into human population has been proven by a study published in 2015 by Lanying Du, Shibo Jiang, Zhengli Shi, Ralph Baric, and Fang Li[14]. Clearly, at that time, they have already acquired the most essential knowledge in Spike engineering:

"*Viral adaptation to human cellular proteases is critical for viral infection of human cells because human cellular proteases, particularly endosomal proteases, are more reliable sources than some extracellular proteases to activate viral entry. Previous research also identified two mutations in SARS-CoV spike that led SARS-CoV to transmit from palm civets to humans. These mutations increased the capability of SARS-CoV spike to bind human receptor angiotensin-converting enzyme 2. Thus, different entry factors appear to have played the most critical roles in the cross-species transmission of MERS-CoV and SARS-CoV: adaption to human cellular proteases by MERS-CoV and adaption to human receptor by SARS-CoV.*"[14]

Intriguingly, this understanding by the above experts has been precisely mirrored in the reality of SARS-CoV-2 Spike: having a designed and engineered RBM and an inserted human protease-cleavage site.

Page 14

1. **On methods of a literature review.** Typically, the scientific description of the steps to create a transmissible virus (as per the chart on page 15) would require biosecurity review before publication in a reputable scientific journal, as this is a dual-use concern,[40] which has the potential to lower barriers toward biological weapons development. However, it should be noted that the steps described by Yan et al are not individually novel and, in our judgment, do not present a biological weapons risk, particularly as the methods chosen have been supplanted by more accurate genetic engineering tools.

Response: This comment by Warmbrod et al. showcased their poor judgement and inability of logical thinking.

First, the experimental steps being novel or not has nothing to do with whether or not the postulated pathway is valid. There is no logical connection between the two; using novel methods is a not a prerequisite for the creation of a novel pathogen.

Also, Warmbrod et al.'s description that other genetic engineering methods are more accurate than the ones presented in our report is mistaken. Both the traditional and the newer genetic engineering tools are accurate. Furthermore, as shown in our above responses, top experts in coronavirus research continue to use the methods we described in their work[22,31].

The pathway that we illustrated in our report was our postulative reconstruction of the laboratory creation of SARS-CoV-2, which was based on the genetic evidence we identified, literature support, as well as our expertise in virology, molecular biology and structural biology.

Importantly, as implied in this review comment, Warmbrod et al. had to agree with our conclusion that the laboratory creation of SARS-CoV-2 is convenient and can be accomplished by following proven concepts and using established techniques. The validity of our postulated pathway is therefore irrefutable.

Second, in our first report, which Warmbrod et al. "reviewed" here, we had not, for once, described SARS-CoV-2 as a bioweapon. Note that, although we concluded SARS-CoV-2 as an unrestricted bioweapon in our second report, that report was published after Warmbrod et al. published this "peer review". It is therefore interesting that Warmbrod et al. brought the term "bioweapon" out twice in this comment of theirs. Their denial of the possibility that this "bioweapon" (a term we never brought up in our first report) could be created in a lab using established methods is clearly baseless. However, the fact that they publicly stated this denial despite that it is baseless is intriguing. In fact, this comment of theirs may be the most important clue for uncovering Warmbrod et al.'s motives in "volunteering" as "peer reviewers" here.

Finally, as shown in their comment, it is their judgement that the postulated steps, which they essentially admit as valid and would successfully yield SARS-CoV-2, "do not present a biological weapons risk". This judgement is clearly in odds with the reality, where SARS-CoV-2 had led to a world-wide pandemic, over 2 million deaths, and devastating social and economic disorders. Their judgement could not be poorer.

In our second report[5], we have defined SARS-CoV-2 as an unrestricted bioweapon, which was based on the evidence of lab creation, the planned cover-up by the CCP government before the initial outbreak, and the characteristics of COVID-19 disease. Importantly, we also described in section 4.3 there how SARS-CoV-2 meets all criteria of a bioweapon described in 2005 by a military bioweapon expert, Dr. Ruifu Yang[5]:

- *It is significantly virulent and can cause large scale casualty.*
- *It is highly contagious and transmits easily, often through respiratory routes in the form of aerosols. The most dangerous scenario would be that it allows human-to-human transmission.*
- *It is relatively resistant to environmental changes, can sustain transportation, and is capable of supporting targeted release.*

Among the four "peer reviewers" here, Nancy Connell and Gigi Gronvall both carry titles, which suggest that they are experts in biodefense. However, as evident in these comments, both of these "experts" are highly deficient in their knowledge in all relevant areas of biology: virology, molecular biology, structural biology, biochemistry, and evolutionary biology. It is also clear that they lack the ability of logical thinking and have very poor judgement. Not only they could not see the genetic, structural, evolutionary evidence that clearly show a laboratory origin of SARS-CoV-2, but also they failed miserably in recognizing SARS-CoV-2 as a bioweapon when it meets the criteria and has fundamentally disrupted the world's social and economic orders. Connell and Gronvall are clearly not what their titles suggest. They are completely incompetent and far behind their times.

Page 16

1. **On troubleshooting molecular cloning.** Line 16: The authors' statement that there is "almost no risk of [molecular cloning] failing"[10] contradicts experience with the technique, as it can be a finicky method[41] requiring keen problem-solving skills.[42]

Response: This is another laughable comment by Warmbrod et al. Molecular cloning is a routine laboratory technique. It is not exaggerating to say that molecular cloning is only finicky to under-trained hands. Any experienced molecular biologist would be competent to accomplish this cloning swiftly. These "reviewers" from the *Johns Hopkins Center for Health Security* clearly have no hands for molecular biology. Again, they have no qualifications at all as reviewers here.

2. **Virology protocol inaccuracies.** Lines 25-29: The report inaccurately describes some common laboratory techniques. For example, the report states that sequence information for short segments of coronavirus RNA-dependent RNA polymerase (RdRp) is possible due to the availability of a polymerase chain reaction (PCR) protocol used to identify coronaviruses. However, PCR is not a sequencing method, it only amplifies existent sequences. PCR is a common tool, used to determine if a specific DNA sequence is in a sample and, if so, how many copies of that sequence are in the sample. Using PCR to detect the presence of coronaviruses in a sample is a standard practice in research and clinical laboratories using standard coronavirus- specific primers, as the RdRp is highly conserved between coronaviruses. Approximately 28 current SARS-CoV-2 diagnostics[43] with Emergency Use Authorization use this method and this specific gene target.

Response: This comment is mistaken and shows that Warmbrod et al. lack the most basic knowledge in biological research. We have never said or implicated that PCR alone was a sequencing method. However, it is common knowledge that DNA products after PCR amplification can be conveniently sequenced. More importantly, when detecting coronaviruses from raw fecal samples, PCR amplification is the necessary first step before DNA sequencing. This protocol (RT-PCR followed by DNA sequencing) has been used by the Shi lab consistently and has been described numerous times in Shi's publications[7,23,25,26,33]. Our description in the report was consistent with this fact:

"*Dr. Zhengli Shi's laboratory uses a PCR protocol, which amplifies a particular fragment of the RdRp gene, as their primary method to detect the presence of coronaviruses in raw samples (bat fecal swap, feces, etc). As a result of this practice, the Shi group has documented the sequence information of this short segment of RdRp for all coronaviruses that they have successfully detected and/or collected.*"[1]

Based on Shi's published work, any qualified scientist would agree that the Shi lab routinely obtain the sequence information from such PCR products. Clearly, Warmbrod et al. are not such scientists.

Page17

1. **Serial passaging and virulence.** Lines 19-20: Serial passaging refers to a process wherein a stock viral population is used to infect an animal, then virus from that animal is collected and used to infect another animal for a designated number of "passages." Serial passage of a virus causes the population to adapt to the animal or cell type in which it is being passaged. Passaging would lead to adaptation to another animal (if passaged *in vivo*) or, if *in vitro*, to the specific cell type used. Most human cells used in laboratory culture have significant differences compared to the commensurate cells in humans. Serial passage, then, would not necessarily make a virus more pathogenic to live humans. Additionally, passage does not necessarily increase fitness of a viral population. The report mischaracterizes the complexity of these processes and projects outcomes from passaging that are not supported by laboratory techniques.

Response: Here, Warmbrod et al. overstated the uncertainty of serial passage. If this comment reflects their honest opinion, then their misjudgement must be due to their complete lack of wet lab experience in serial passage.

There are plenty of examples where serial passage has allowed successful adaptation of a virus to infect a novel host with significant lethality[34-37]. Using serial passage, Dr. Li-Meng Yan had previously converted influenza A H3N2/Hong Kong/1/68 virus, which is not lethal to mice, to a novel strain that causes efficient infections and high lethality in mice[35]. Dr. Ralph Baric also used serial passage to successfully convert a strain of SARS virus into a desired mouse-adapted strain[34]. Warmbrod et al.'s knowledge on serial passage is completely out of line with the reality as evidenced by the literature.

In addition to driving the viral strain(s) toward optimal fitness and desired lethality, serial passage also has the benefit of partially mimcking natural evolution and thereby can possibly remove some traces of genetic manipulation.

The basis for high affinity and high pathogenicity of SARS-CoV-2 may have been determined at an earlier stage, specifically the genetic manipulation of Spike (RBM swap and FCS insertion). Serial passage further optimizes the adaptation of the virus toward human ACE2 receptor *in vivo*, however, without the need to significantly improve affinity and/or pathogenicity; the molecular basis for both properties should have been established previously.

Using hACE2 mice for serial passage, as postulated in our report, would be the most convenient, efficient, and inexpensive way of driving the hACE2-oriented adaptation. However, not all pathogenic properties of SARS-CoV-2 associated with human infections could be shown faithfully in this mouse model because of the species differences. Transmissibility is one such property. Dr. Li-Meng Yan has shown that golden hamsters are a great animal model for characterizing the transmissibility of SARS-CoV-2. If the CCP scientists responsible for the SARS-CoV-2 creation and validation had used golden hamsters to evaluate the viral transmissibility, they might have then come to a more accurate estimation of the transmissibility and would not have described the initial outbreak in Wuhan as "controllable".

Page 18

1. **Unrealistic timelines.** Lines 25-29: The timeline offered for how an entirely novel protein can be engineered in a little studied virus, circa 2019, is not scientifically realistic.

Response: Contrary to the reviewers' comment, coronaviruses are well studied. The lack of knowledge by Warmbrod, West, Connell, and Gronvall has been consistently shown in every comment and throughout the review.

In fact, the Spike proteins of coronaviruses are well studied. So much has been learned on Spike, including atomic details of its interaction with hACE2 revealed by high-resolution structures[22,38], that the Spike from ZC45/ZXC21 should not be considered as entirely novel. Importantly, genetic engineering of Spike has been done repeatedly in the past[6,7,10], where a Spike of a bat coronavirus would be successfully converted into a novel Spike capable of binding hACE2 and thereby establishing infection in human cells. Dr. Fang Li used less than two months to accomplish the following: RBM-swapping, Spike (RBD) engineering, and solving the crystal structure of the novel RBD in complex with hACE2 (their manuscript was submitted to *Nature* on Feb 16th, 2020)[22]. In our report, we estimated the time for completing the RBM swap as 1.5 months. Note that our postulated step here does not involve protein crystallization, diffraction data collection, structure solution, model building, refinement, or manuscript preparation, which Dr. Fang Li and colleagues did go through for their *Nature* publication[22]. The timeline we offered is scientifically sound and reasonable. Warmbrod et al.'s comment here, however, is clearly mistaken.

Page 19

1. **Methods of genetic modification in viruses.** Lines 11-12: The authors incorrectly state that reverse genetics systems are commonly used to assemble coronaviruses. Reverse genetics[44] can be used in other virus synthesis, such as influenza. The paper the authors cite, from Thao and colleagues,[41] did use reverse genetics in a yeast-based system to synthesize full length SARS- CoV-2. However, previous research[45] had identified that coronaviruses can be particularly difficult to engineer using reverse genetics systems, as the large size of Nidovirus genomes, replicase activity, and requirement for large transcript synthesis create obstacles. Certain methods require insertion of mutations elsewhere in the genome to manage the T7 transcription termination signals or require helper viruses to coinfect cells to aid in cloning. Recent work

in dengue viruses[46] and MERS[47] has shown the promise of Gibson assembly in synthesizing positive-strand viruses.

Response: This is yet another ignorant comment made by these "reviewers". Reverse genetics have been used repeatedly to assemble coronavirus genomes[9,12,13,39-41]. Our statement was accurate and supported by the vast literature. Warmbrod et al. have no qualifications whatsoever in serving as reviewers here.

2. **Reverse genetics tools (and limitations).** Lines 22-24: Reverse genetics and synthetic biology provide technological tools to synthesize SARS-CoV-2, as demonstrated by the methods section of the Thao paper.[41] The yeast used for this synthesis of SARS-CoV-2 used a specific platform that depended on a mouse hepatitis virus. The description in Yan et al of pooling the DNA fragments together and "transforming" them into yeast will not work,[48,49] as it would require a method known as transformation-associated recombination,[50] calling into question the Yan analysis.

Response: If this is an honest comment, then Warmbrod et al. had no idea what they were talking about. They argued that "*pooling the DNA fragments together and 'transforming' them into yeast will not work, as it would require a method known as transformation-associated recombination*". This judgement is proven wrong. The reference we cited here did just that to construct the SARS-CoV-2 genome[42]: they pooled the DNA fragments together and transformed them into yeast. This exact procedure is termed *transformation-associated recombination in yeast*. It is shocking that Warmbrod et al. managed to embarrass themselves this much.

To readers who were misled by Warmbrod et al., this yeast-based reverse genetic system relies on the homologous recombination machinery in yeast cells to synthesize the full genome of SARS-CoV-2. Therefore, as long as viral genomic DNA fragments with overlapping sequence that shares homology on both ends and the YAC vector fragments are co-transfected, the homologous recombination machinery in yeast will assemble the whole viral genome. Vectors containing the desired whole viral genome can then be selected, amplified, and isolated. Contrary to what has been suggested by Warmbrod et al., this method is independent of any viral platform because it is a cloning method to synthesize DNA by using the *in vivo* recombination machinery of budding yeast. As mentioned in the reference in our report, this method had been used, before the SARS-CoV-2 pandemic, to successfully synthesize a DNA virus with a large viral genome[43]. The same method had also been used in 2020 to synthesize the SARS-CoV-2 genome[42].

Also, in addition to this yeast-based method, we have stated in the report that other methods of reverse genetics are also well established and could be used as well. Literature clearly shows that many reverse genetics methods are available and have been successfully implemented by coronavirus experts[9,12,13,39-41].

Warmbrod et al. once again muddled the water on a subject that they had no knowledge in whatsoever. Considering the relevance of the topic to public health and national security, their behaviors can be safely described as irresponsible and even despicable.

3. **On viral passaging and adaptation.** Lines 34-35: Adaptation for receptors likely improves infectability of a virus, but it does not necessarily make the virus more transmissible, pathogenic, or virulent. Even if the virus adapts for the receptor, it does not mean that the virus will be able to cause viremia or transmit to other hosts. The report falsely asserts that serial passage would "validate the virus' fitness and ensure its receptor-oriented adaptation toward its intended host"[10] and also argue a contradictory theory on page 3 that the virus *was not* serially passaged. While viral passaging can optimize viral fitness, this is never a guarantee and has to be scientifically demonstrated.

Response: Warmbrod et al. once again distorted our report and at the same time were mistaken in every single point they raised here.

First, we never described receptor-oriented adaptation in serial passage as the sole step to decide transmissibility, pathogenicity, or virulence. As we have described in one of our earlier responses, the molecular bases of high affinity, pathogenicity, and virulence should have been largely set by the genetic engineering of Spike. However, serial passage would be set up in a way that strains with improved affinity and virulence could be selected and developed further. This process, which enhances affinity, could have, to some extent, also enhanced transmissibility. Also, importantly, serial passage is necessary as it ensures that the virus is optimized as a whole (individual components of it have been derived separately) for *in vivo* replication and fitness. It also ensures that the genome is stabilized. For an artificial viral pathogen aimed at destruction, it is important that its genome is stable and the virus does not attenuate quickly in the intended host. Therefore, our statement that serial passage would validate the virus' fitness and ensure its receptor-oriented adaptation to its intended host is justified and accurate.

Second, Warmbrod et al. distorted our description on page 3 and thereby created room to insert their otherwise unjustified criticism. Our original description was that the furin-cleavage site "*must have been inserted into the SARS-CoV-2 genome artificially by techniques other than simple serial passage .....*". Clearly, we meant that the artificial insertion of FCS could not be done using serial passage. We have never said that the virus was not serially passaged. The intentional distortion of our report by Warmbrod et al. had shown repeatedly in their comments, which spells out the sinister nature of their motives in "volunteering" as "reviewers" here.

Finally, Warmbrod et al. argued that the classical method serial passage would not be able to guarantee optimization of viral fitness. This is a pretentious comment, which shows Warmbrod et al.'s superficial understanding of serial passage. We would bet that Warmbrod et al. will not be able to optimize viral fitness using serial passage in a lab. However, it would be so only because they are clearly incompetent scientists and have no wet lab experience in serial passage. We remain fully confident in stating that serial passage can be used to improve and optimize viral fitness.

4. **SARS-CoV-2 animal models.** Line 39: Finding an animal model for SARS-CoV-2 has been difficult[51] and, before 2020, there was not a good animal model for SARS-CoV, so the idea of "serial passage in laboratory animals"[10] would have been challenging.

Response: This is yet another shockingly ignorant comment by Warmbrod et al. Many animal models have been used for studying SARS[44-46]. Many models have also been used to study SARS-CoV-2 right after the pandemic started[47-49], which is clearly in odds with their comment that "*(f)inding an animal model for SARS-CoV-2 has been difficult*".

Their comment that serial passage in laboratory animals would have been challenging is also mistaken. The opposite is true as evidence by the literature[34-37].

It is noteworthy though that, although animal models are readily available, no single animal model would be perfect and show all pathogenic characteristics of SARS-CoV-2 infections in humans. It is, after all, a model.

The comment once again shows the complete lack of qualification of Warmbrod et al. as reviewers.

Page 20

1. **Serial passaging and virulence.** Lines 2-4: The authors incorrectly assert that serial passage of a virus only leads to increased virulence. The report asserts that 10 to 15 rounds of passage would improve the viral Spike protein's binding affinity and the infectivity and lethality of the virus. However, serial passaging does

not always lead to genome stabilization, as some viral populations may die off.[52] Of the strains that do stabilize, infection efficiency is only enhanced for the model species used for passaging, not for all species. Some of these (millions of) virions may be more lethal or infectious, just as many may be less so. Passaging cannot guarantee an outcome of viral evolution. The life cycle of a virus and infection efficiency depend on more than just receptor binding, and adaptation to 1 organ or 1 type of receptor may come at the expense of reduced ability to spread to other organs, cause viremia, shed from 1 host, or cause pathogenicity.[53] Thus, improved receptor binding does not necessarily mean enhanced transmissibility or pathogenicity.[54]

Response: Warmbrod et al. showed, once again, their lack of understanding of serial passage. Serial passage is not an experiment that runs on a natural course. There is targeted experimental design (e.g. the use of hACE2-mice), which sets a direction for viral adaptation. There is also selection, which filters out the unwanted strains and enriches the ones with the desired property. Depending on the goal of the experiment, one can select for more lethal strains or less lethal ones. Unlike what Warmbrod et al. described here, we have never said that serial passage of a virus only leads to increased virulence. However, we do assert that, if increased virulence is the goal, it can be successfully achieved by a proper serial passage experiment. The comment by Warmbrod et al. here is, once again, false and misleading.

Also, we have never stated that receptor binding dictates transmissibility or pathogenicity. We have commented on receptor-binding, transmissibility, and pathogenicity in previous responses and will not repeat it here again.

However, we do want to reiterate that, although receptor-binding is an important goal of the adaptation, serial passage does not only optimize the virus on receptor-binding. It is also a necessary step to optimize the overall fitness, the replication efficiency, and the pathogenicity of the virus *in vivo*.

2. **On laboratory adaptation leading to increased virulence.** Lines 16-21: Viral adaptation can include attenuation. That is one reason why viruses and bacteria are sometimes serially passaged for attenuation to be used in vaccines.[55,56] It cannot be stated as Yan and colleagues do that there is a "lack of apparent attenuation"[10] so far in this pandemic, because the global incidence of COVID-19 (especially asymptomatic cases) is unknown, or that viral adaptation, *in vitro* or *in vivo*, led to increase transmissibility or virulence.

Response: Contrary to Warmbrod et al.'s criticism, our description that there is a "*lack of apparent attenuation of SARS-CoV-2 so far despite its great prevalence*" has been proven to be the reality. The pandemic has been going on for over a year and yet there is no apparent attenuation of the virus. In fact, a very recent finding strengthened our point even further[50]: the later emerged, dominant strain showed enhanced infectivity, fitness, and transmission. It is again clear which side has the truth and which side has been consistently mistaken.

3. **Viral mutation rates.** Line 24: The authors state that if serial passage is confined to 1 species, less random mutations occur, but this is incorrect. Mutation rates are a function of the RdRp, as well as the ExoN proofreading enzyme,[57] and so repeated passage will not inherently make a virus more or less likely to mutate. However, passage does affect which mutations[58] become fixed in the viral population. Coronaviruses form a quasispecies, where each variant within the population can be different from the others and have different fitnesses. Together, the population of variants infect a host, disseminate from the initial infection site, and cause pathogenesis. During a passage, the viral variants best suited for infection and pathogenesis within the model organism are selected for, but the rate of mutations occurring does not change. Because mutations can still occur, there is a possibility the virus can adapt, unless the mutations cause so many deleterious mutations that the population collapses.

Response: We have never stated or implicated in our report that, "*if serial passage is confined to 1 species, less random mutations occur*". We never linked the number of species in serial passage to the rate of mutation. This is, again, another shameful distortion of our report by Warmbrod et al.

The rest of the comment seems to be a pointless muttering rather than an articulation of anything.

Page 21 (Conclusion)

1. While the impact of SARS-CoV-2 on global public health is undeniable, the pathogenic effects of SARS-CoV-2 infection at an individual or cellular level are not unprecedented. Many viruses are capable of causing high morbidity and mortality,[59,60] infecting several organs, and/ or presymptomatic or asymptomatic transmission.[61] Additionally, other viral infections (eg, chikungunya) also induce long-term sequelae.[62] Humans have contended with many scourges and it is a certainty that COVID-19 will not be the last.

Response: Warmbrod et al. again distorted the meaning of our report, although this time they did it more subtly. Our exact words here were:

"*The characteristics and pathogenic effects of SARS-CoV-2 are unprecedented. The virus is highly transmissible, onset-hidden, multi-organ targeting, sequelae-unclear, lethal, and associated with various symptoms and complications.*"

Clearly, the word "*unprecedented*" here was used to describe the collective characteristics and pathogenic effects caused by SARS-CoV-2. Warmbrod et al., however, listed different viruses, each showing one or two of these effects, and used them as counter evidence of our argument. The fact that they could not come up with a proper example to support their own argument indeed proves our statement that the characteristics and pathogenic effects of SARS-CoV-2 are unprecedented.

Furthermore, the impact of SARS-CoV-2 is not limited to just pathogenicity and global health. The scale of destruction in social orders and economy caused by COVID-19 is also unprecedented. For a novel pathogen with such an impact, the question of its origin should not be answered lightly.

However, unfortunately, since the beginning of the pandemic, the theory of SARS-CoV-2 having a natural origin has been promoted widely even though the evidence for it is very weak and often omitted in such promotions. Gigi Gronvall, one of the four "peer reviewers" here, is among the scientists who were engaged in pushing the natural origin theory since the beginning of the pandemic[51]. A great deal of their efforts here was directed at suppressing the lab origin theories and degrading them into "conspiracy theories" to mislead the public. This review published by Gronvall and colleagues here serves the same purpose.

However, as revealed by these comments, Gronvall and the three other "reviewers" have severe deficiency of knowledge in every branch of biology that is relevant to our report: virology, molecular biology, structural biology, biochemistry, and evolutionary biology. It is shameful and utterly irresponsible for Gronvall et al. to produce a review on our report when they are completely unqualified to do so. They also intentionally distorted our reports on multiple occasions and then inserted their otherwise-unjustified criticisms. Importantly and aggravatingly, what is being muddled by their despicable behaviors is the most urgent question that the world is facing – what is the true origin of the COVID-19 pandemic.

Through these comments, Gronvall and her three colleagues have thoroughly proved that they are shoddy scientists who should not be trusted in the discussion of the origin of SARS-CoV-2. It has also become evident that there is no evidence to prove a natural origin for SARS-CoV-2.

The other thing that Gronvall et al. succeeded in achieving here is to prove to the world that the Yan reports are unshakable scientifically.

As we have concluded in our second report[5], the evidence collectively indicates that SARS-CoV-2 is an *Unrestricted Bioweapon* developed by the CCP government and that its release to the human population was a planned execution. The world has to face this truth and treat SARS-CoV-2 for what it really is. Compromising on this issue entails prolonged suffering of the human race and continued social and economic loss. It would also signify the success of the CCP's "perfect crime", which may encourage the CCP and possibly other regimes to launch future attacks using other *Unrestricted Bioweapons*.

Our two reports, which so far could not be challenged by anybody scientifically, hold the truth to the COVID-19 pandemic. Our upcoming report will be produced to this same standard. These reports need to be treated seriously if the world wants to look in the right direction to find the true origin of this pandemic.

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