



October 20, 2021

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

Dear Chair McMorris Rodgers:

Thank you for your continued interest in the work of the National Institutes of Health (NIH). I am writing today to provide additional information and documents regarding NIH's grant to EcoHealth Alliance, Inc.

It is important to state at the outset that published genomic data demonstrate that the bat coronaviruses studied under the NIH grant to EcoHealth Alliance, Inc. and subaward to the Wuhan Institute of Virology (WIV) are not and could not have become SARS-CoV-2. Both the progress report and the analysis attached here again confirm that conclusion, as the sequences of the viruses are genetically very distant.

The fifth and final progress report for Grant R01AI110964, awarded to EcoHealth Alliance, Inc. is attached with redactions only for personally identifiable information. This progress report was submitted to NIH in August 2021 in response to NIH's compliance enforcement efforts. It includes data from a research project conducted during the 2018-19 grant period using bat coronavirus genome sequences already existing in nature.

The limited experiment described in the final progress report provided by EcoHealth Alliance was testing if spike proteins from naturally occurring bat coronaviruses circulating in China were capable of binding to the human ACE2 receptor in a mouse model. All other aspects of the mice, including the immune system, remained unchanged. In this limited experiment, laboratory mice infected with the SHC014 WIV1 bat coronavirus became sicker than those infected with the WIV1 bat coronavirus. As sometimes occurs in science, this was an unexpected result of the research, as opposed to something that the researchers set out to do. Regardless, the viruses being studied under this grant were genetically very distant from SARS-CoV-2.

The research plan was reviewed by NIH in advance of funding, and NIH determined that it did not fit the definition of research involving enhanced pathogens of pandemic potential (ePPP) because these bat coronaviruses had not been shown to infect humans. As such, the research was not subject to departmental review under the HHS P3CO Framework. However, out of an abundance of caution and as an additional layer of oversight, language was included in the terms and conditions of the grant award to EcoHealth that outlined criteria for a secondary review, such as a requirement that the grantee report immediately a one log increase in growth. These

measures would prompt a secondary review to determine whether the research aims should be re-evaluated or new biosafety measures should be enacted.

EcoHealth failed to report this finding right away, as was required by the terms of the grant. EcoHealth is being notified that they have five days from today to submit to NIH any and all unpublished data from the experiments and work conducted under this award. Additional compliance efforts continue.

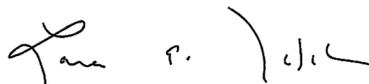
The second document is a genetic analysis demonstrating that the naturally occurring bat coronaviruses used in experiments under the NIH grant from 2014-2018 are decades removed from SARS-CoV-2 evolutionarily. The analysis compares the sequence relationships between:

- SARS-CoV-1, the cause of the SARS outbreak in 2003;
- SARS-CoV-2, the cause of COVID-19 pandemic;
- WIV-1, a naturally occurring bat coronavirus used in experiments funded by the NIH;
- RaTG13, one of the closest bat coronavirus relatives to SARS-CoV-2 collected by the Wuhan Institute of Virology; and
- BANAL-52, one of several bat coronaviruses recently identified from bats living in caves in Laos.

While it might appear that the similarity of RaTG13 and BANAL-52 bat coronaviruses to SARS-CoV-2 is close because it overlaps by 96-97%, experts agree that even these viruses are far too divergent to have been the progenitor of SARS-CoV-2. For comparison, today's human genome is 96% similar to our closest ancestor, the chimpanzee. Humans and chimpanzees are thought to have diverged approximately 6 million years ago.

The analysis attached confirms that the bat coronaviruses studied under the EcoHealth Alliance grant could not have been the source of SARS-CoV-2 and the COVID-19 pandemic.

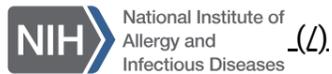
If you or your staff have questions, NIH would be pleased to brief you on these documents.



Lawrence A. Tabak, D.D.S., Ph.D.
Principal Deputy Director

COVID-19

Get the latest public health information from CDC [↗](https://www.cdc.gov/coronavirus) (<https://www.cdc.gov/coronavirus>). | Get the latest research information from NIH [↗](https://covid19.nih.gov/) (<https://covid19.nih.gov/>). [Información de NIH en español](https://salud.nih.gov/covid-19/) [↗](https://salud.nih.gov/covid-19/) (<https://salud.nih.gov/covid-19/>).



SARS-CoV-2 and NIAID-supported Bat Coronavirus Research

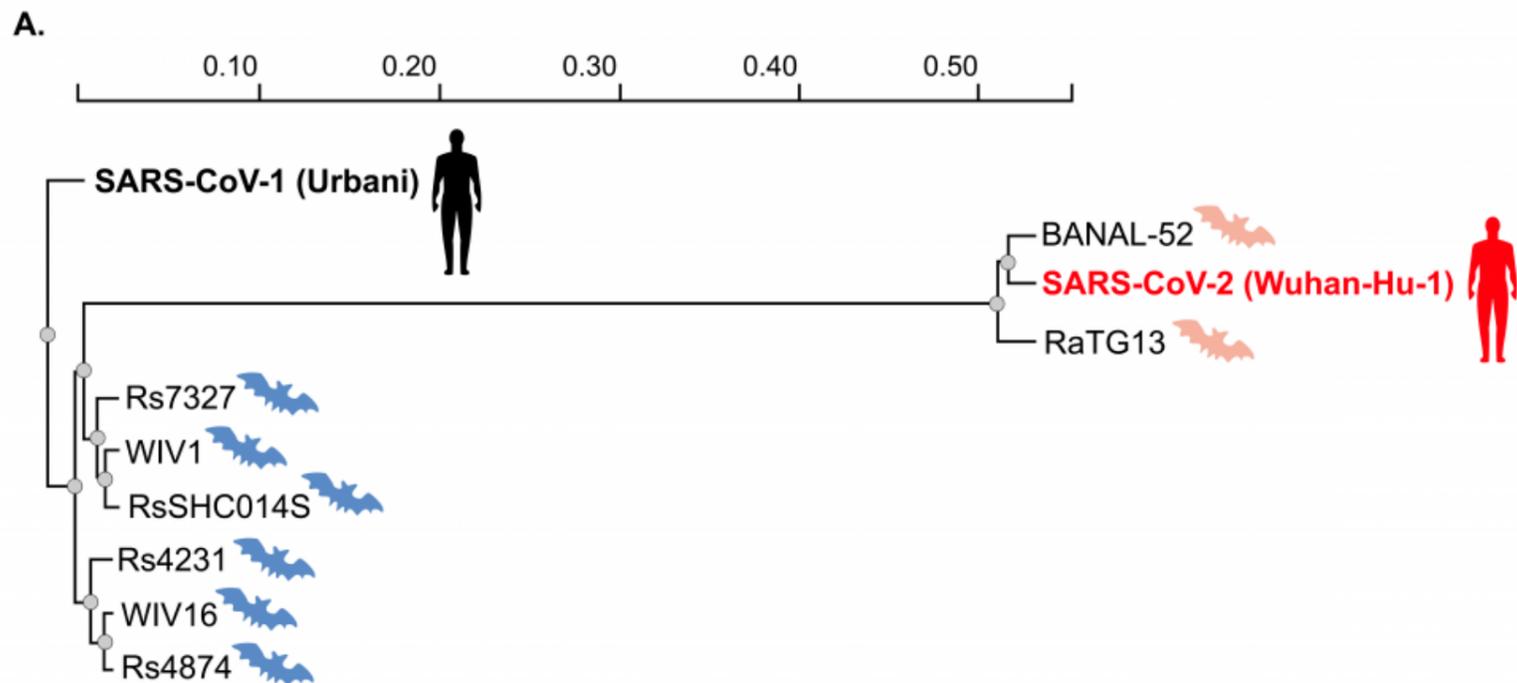
An Analysis: Evolutionary Distance of SARS-CoV-2 and Bat Coronaviruses Studied Under the NIH-supported Research Grant to EcoHealth Alliance

The research that NIH approved under the grant to EcoHealth Alliance with a subaward to the Wuhan Institute of Virology in Wuhan, China sought to understand how animal coronaviruses, especially bat coronaviruses, evolve naturally in the environment and have the potential to become transmissible to the human population. This research included studying viral diversity in bat reservoirs, surveying people who work in live animal markets or other occupations with high exposure to wildlife for evidence of bat coronavirus infection and analyzing data to predict which newly discovered viruses pose the greatest threat to human health.

Coronaviruses use a protein called spike to bind to a protein on the surface of a host cell to facilitate infection. Some coronaviruses, including SARS-CoV-1 (the cause of the SARS outbreak in 2003) and SARS-CoV-2 (the cause of the COVID-19 pandemic), use the angiotensin converting enzyme-2 (ACE2) protein to help enter and infect host cells. In order to study animal coronaviruses circulating in nature, the investigators replaced the spike protein from a well-characterized bat coronavirus, WIV1-CoV, with the spike protein of animal coronaviruses recently discovered in bats in China. Using techniques common in virology, experiments involved a single round of infection in several cell lines, and in some cases, in mice that were genetically modified to express the human version of ACE2. All other aspects of the mice, including the immune system, remained unchanged. The ACE2 transgenic mice were used to determine if spike proteins from bat coronaviruses discovered in China were capable of binding human ACE2, and therefore, whether the bat coronaviruses themselves, which were already present in the environment, could potentially infect humans and cause disease. WIV1-CoV is not known to cause infection in humans but has been shown in the laboratory to infect both human cells and ACE2 transgenic mice ([ref ↗](http://www.nature.com/articles/nature12711) (<http://www.nature.com/articles/nature12711>)), making it an ideal tool to use for these studies. Several of the bat coronaviruses used in these experiments were also found to be capable of replicating in ACE2 transgenic mice, indicating that the spike protein from the naturally occurring bat coronaviruses from which they were made could bind ACE2 in vivo.

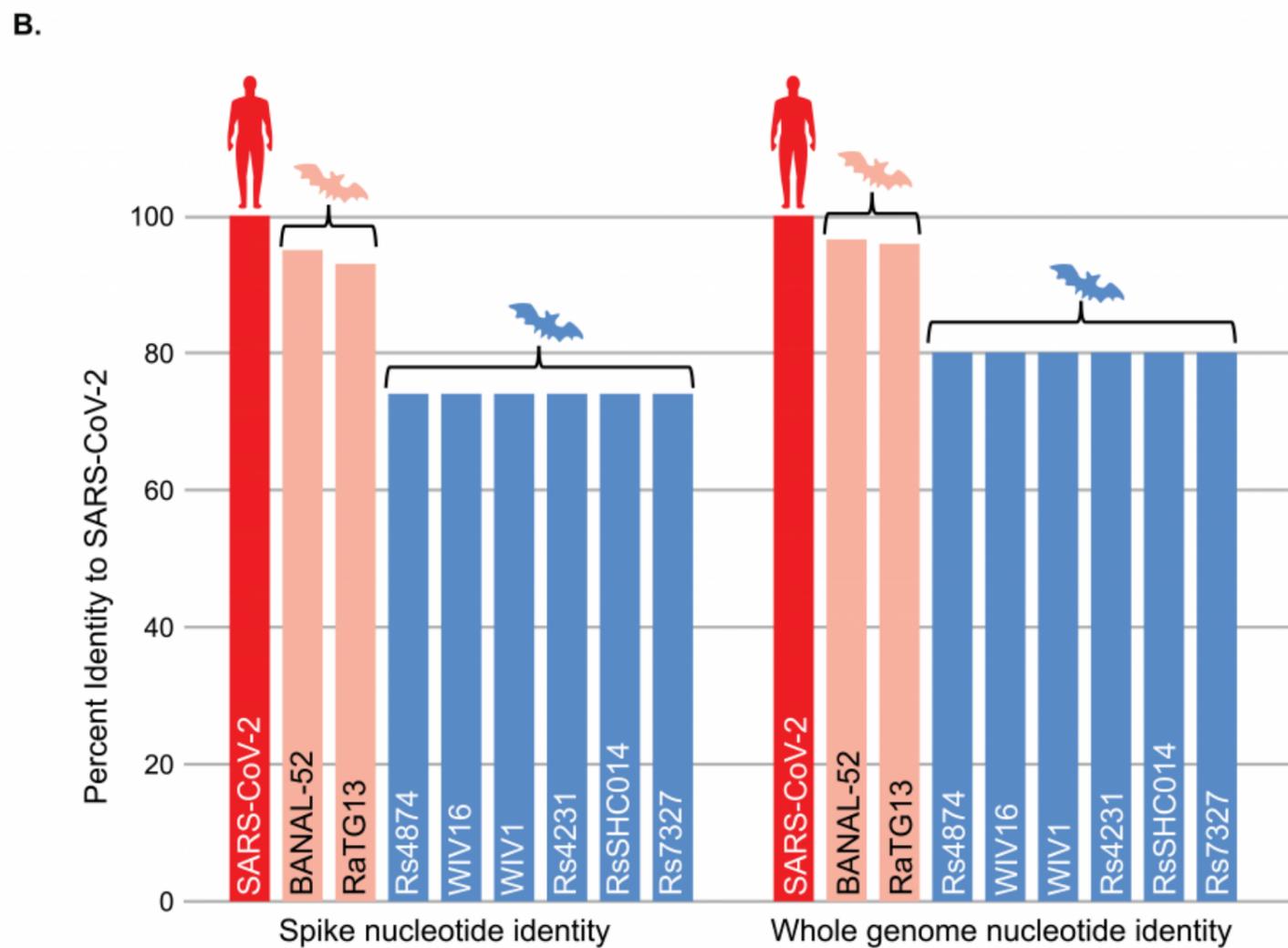
Questions have been raised about whether this NIH-funded research had a role in the emergence of SARS-CoV-2. In this regard, the chimeric viruses that were studied (i.e., the WIV-1 virus with the various spike proteins obtained from bat viruses found in nature) were so far distant from an evolutionary standpoint from SARS-CoV-2 (Figure 1) that they could not have possibly been the source of SARS-CoV-2 or the COVID-19 pandemic. The body of the scientific data from this award including the bat coronavirus sequences published in the scientific literature and public databases makes this conclusion readily apparent to anyone with experience in and knowledge of virus phylogeny and evolutionary biology.

Figure 1. Relationship of bat coronaviruses to SARS-CoV-1 and SARS-CoV-2.



A) A phylogenetic tree based on nucleotide sequences of indicated coronavirus spike proteins demonstrating the evolutionary distance of SARS-CoV-2 with the bat coronaviruses experimentally studied under the NIH grant to EcoHealth Alliance (blue bat icons). Bat coronaviruses most closely related to SARS-CoV-2, none of which were studied in the EcoHealth grant, are denoted with orange bat icons. The scale bar represents the number of nucleotide substitutions per site.

Credit: NIAID



B) Comparison of the nucleotide sequence identity of indicated coronaviruses to SARS-CoV-2. The left panel shows the percent identity of indicated coronavirus spike nucleotide sequences to SARS-CoV-2. The right panel shows the percent nucleotide identity of the indicated full coronavirus genomes to SARS-CoV-2.

Despite the similarity of RaTG13 and BANAL-52 bat coronaviruses (orange bars) to SARS-CoV-2 (red bars), experts agree that even these viruses are far too divergent to have been the progenitor of SARS-CoV-2, further highlighting that the bat coronaviruses studied under the EcoHealth

Alliance grant (blue bars) could not have been the source of SARS-CoV-2 and the COVID-19 pandemic. Several other similarly divergent viruses that failed to replicate in cells are not shown ([ref !\[\]\(2e897e890e69d81eae4503a8342c36b0_img.jpg\) \(https://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1006698\)](https://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1006698)).

Credit: NIAID

The above figure shows the sequence relationships between SARS-CoV-1, SARS-CoV-2 and the naturally occurring bat coronaviruses used in experiments under the NIH grant to EcoHealth Alliance and reported in the scientific literature ([ref !\[\]\(e2376d476d06eb31946dc01a69a4403a_img.jpg\) \(http://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1006698\)](http://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1006698)) or annual progress reports. From this analysis, it is evident that the viruses studied under the EcoHealth Alliance grant are very far distant from SARS-CoV-2. Included for comparison is RaTG13, one of the closest bat coronavirus relatives to SARS-CoV-2 collected by the Wuhan Institute of Virology ([ref !\[\]\(bbb3388d591ef640dd8a8c4262f2866a_img.jpg\) \(http://www.nature.com/articles/s41586-020-2012-7\)](http://www.nature.com/articles/s41586-020-2012-7)) and BANAL-52, one of several bat coronaviruses recently identified from bats living in caves in Laos ([ref !\[\]\(ef6e697e79b33cfafe8ba6744dc11bd6_img.jpg\) \(http://www.researchsquare.com/article/rs-871965/v1\)](http://www.researchsquare.com/article/rs-871965/v1)). Although RaTG13 and BANAL-52 are 96-97% identical to SARS-CoV-2 at the nucleotide level (>900 nucleotide differences across the entire genome), the difference actually represents decades of evolutionary divergence from SARS-CoV-2. Experts in evolutionary biology and virology have made it clear that even the closest known relatives of SARS-CoV-2, which were not studied under the EcoHealth Alliance grant, are evolutionarily too distant from SARS-CoV-2 to have been the progenitor of the COVID-19 pandemic ([ref !\[\]\(36a26e5b369c5d231b75de2efc184e39_img.jpg\) \(http://www.cell.com/action/showPdf?pii=S0092-8674%2821%2900991-0\)](http://www.cell.com/action/showPdf?pii=S0092-8674%2821%2900991-0), [ref !\[\]\(c5cee65d8128a7c1c31c4ac9cbd38372_img.jpg\) \(http://www.science.org/content/article/close-cousins-sars-cov-2-found-cave-laos-yield-new-clues-about-pandemic-s-origins\)](http://www.science.org/content/article/close-cousins-sars-cov-2-found-cave-laos-yield-new-clues-about-pandemic-s-origins)). Field studies continue the search for more proximate progenitors.

Content last reviewed on October 20, 2021