

Did COVID-19 originate in a laboratory? Many scientists still harbor questions

Nikolai Petrovsky was scrolling through social media after a day on the ski slopes when reports describing a mysterious cluster of pneumonia cases in Wuhan, China caught his eye. It was early January 2020, and Petrovsky, an immunologist, was at his vacation getaway in Keystone, Colorado, which is where he goes most years with his family to flee the searingly hot summers at home in South Australia. He was soon struck by an odd discrepancy in how the pneumonia cases were portrayed. Chinese authorities and the [World Health Organization](#) were saying there was nothing to worry about, but locals in the area, he says, were posting about “bodies being stretchered out of houses in Wuhan and police bolting apartment doors shut.”

Petrovsky is a professor at Flinders University, near Adelaide, and he is also founder and chairman of a company called Vaxine that develops immunizations for infectious diseases, among other projects. Since 2005, he’s received tens of millions of dollars in funding from the U.S. National Institutes of Health to support the development of vaccines and compounds called adjuvants that boost their effects. After Chinese scientists posted a [draft](#) genome of the novel coronavirus SARS-CoV-2, the disease culprit in Wuhan, Petrovsky — who by this time had put skiing on the backburner to work from his Colorado home office — directed his colleagues down under to run computer modeling studies of the viral sequence, a first step towards designing a vaccine.

This generated a startling result: The spike proteins studding SARS-CoV-2 bound more tightly to their human cell receptor, a protein called ACE2, than target receptors on any other species evaluated. In other words, SARS-CoV-2 was surprisingly well adapted to its human prey, which is unusual for a newly emerging pathogen. “Holy shit, that’s really weird,” Petrovsky recalls thinking.



Immunologist Nikolai Petrovsky studies viruses and develops vaccines and adjuvants. He has pushed back against the idea that considering whether or not SARS-CoV-2 has a laboratory origin is a conspiracy theory. Credit: Vaxine Pty Ltd/Flinders University

As Petrovsky considered whether SARS-CoV-2 may have emerged in lab cultures with human cells, or cells engineered to express the human ACE2 protein, [a letter](#) penned by 27 scientists appeared suddenly on Feb. 19 in the prestigious medical journal The Lancet. The authors insisted that SARS-CoV-2 had a natural origin, and they condemned any alternate hypotheses as conspiracy theories that create only “fear, rumors, and prejudice.”

Petrovsky says he found the letter infuriating. Conspiracy theorists is “the last thing we were, and it looked to be pointing at people like us,” he says.

Last month, a team of international scientists completed a month-long visit to Wuhan to investigate SARS-CoV-2's origins. Convened by the WHO, and closely monitored by Chinese authorities, the team concluded initially that a lab leak was so unlikely that further investigations of it were unnecessary. The WHO's director general later walked that statement back, claiming that "all hypotheses remain open and require further analysis and studies." A group of 26 scientists, social scientists, and science communicators — Petrovksy among them — have now signed their own [letter](#) arguing that WHO investigators lacked "the mandate, the independence, or the necessary accesses" to determine whether or not SARS-CoV-2 could have been the result of a laboratory incident.



Members of the WHO team investigating the origins of the Covid-19 pandemic leave their hotel in Wuhan, China in January 2021. Credit: Hector Retamal/AFP/Getty Images

The WHO investigation follows a year during which debates over SARS-CoV-2's origins turned increasingly acrimonious. Chinese officials were, and still are, unwilling to provide information that might settle lingering questions about where the virus came from, and in the absence of critical data, expert

views coalesced around two competing scenarios: One that a lab leak was plausible and needed more scrutiny, and another that SARS-CoV-2 had almost certainly spilled over from nature and that the odds of a lab leak were so remote that the possibility could essentially be taken off the table. Those insisting on a natural origin say the virus lacks genetic features that would show it to have been deliberately engineered. But it's also possible that SARS-CoV-2 evolved naturally in the wild before it was brought into a lab to be studied, only to subsequently escape. The Wuhan Institute of Virology, which many see as the likeliest site of a breakout, houses [one of the largest](#) collections of coronaviruses in the world.

David Relman, a microbiologist at Stanford University, says a lab leak was never the subject of a “fair and dispassionate discussion of the facts as we know them.” Instead, tempers soon began to flare as those calling for a closer look at possible lab origins were dismissed as conspiracy theorists spouting misinformation. Election-year politics and growing Sinophobic sentiments only added to the tensions. Attacks on Asian Americans had been escalating since the pandemic began, and with then-President Trump fuming about a “Chinese virus,” many scientists and reporters became “cautious about saying anything that might justify the rhetoric of his administration,” says Jamie Metzl, a senior fellow at the Washington, D.C.-based Atlantic Council, an international affairs think tank.



Postdoctoral fellow Alina Chan, who studies gene therapy and cell engineering, has challenged the idea that SARS-CoV-2 could only have natural origins.

Credit: Alina Chan

It could have been career suicide for scientists to voice suspicions about a possible lab leak, says Metzl, especially when there was already a long history of viral disease outbreaks spilling over from nature. Alina Chan, a post-doctoral fellow specializing in gene therapy and cell engineering at the Broad Institute in Cambridge, Massachusetts, echoes that view. Chan says the risk of challenging the orthodoxy that SARS-CoV-2 has natural origins — an entirely plausible hypothesis, she maintains — is greatest for established scientists in infectious disease with supervisory roles and staffs to support. She herself has spent much of the last year calling for more scrutiny of a potential lab leak, claiming that as a post-doc, she has less to lose.

The vitriol also obscures a broader imperative, Relman says, which is that uncovering the virus' origins is

crucial to stopping the next pandemic. Threats from both lab accidents and natural spillovers are growing simultaneously, as humans move steadily into wild places, and new biosafety labs grow in number around the world. “This is why the origins question is so important,” Relman says.

“We need a much better sense about where to place our resources and effort,” he adds. And if a lab release for SARS-CoV-2 looks plausible, Relman says, “then it absolutely deserves a whole lot more attention.”

If SARS-CoV-2 did spill over into humans from the wild, how and where did that happen? A year into the pandemic, these remain open questions. Scientists still speculate about whether the virus passed directly into humans from infected bats (known reservoirs for hundreds of different coronaviruses), or through an intermediary animal species. The Huanan Seafood Wholesale Market in Wuhan was initially thought to be the originating site of a potential spillover, since that’s where the first cluster of Covid-19 — the disease caused by the virus — was detected. But newer evidence suggests that animal or human infections may have been circulating elsewhere for months beforehand, and the focus has since broadened to other markets in the city, [wildlife farms in Southern China](#), and other possible scenarios, such as consuming virally-contaminated frozen meat originating in other provinces.

Importantly, the virus’ immediate ancestors have yet to be identified. The closest known relative, a coronavirus dubbed RaTG13, is genetically 96 percent similar to SARS-CoV-2.

A lab-escaped virus, meanwhile, would have been introduced to the world by a researcher or technician who became infected with it. These sorts of lab leaks have happened before, and were implicated in [several cases](#) of community transmission during SARS outbreaks in the early 2000s. In 2017, the Wuhan Institute of Virology became the first lab in mainland China to receive a Biosafety Level 4 (BSL-4) designation, the highest security status for a research space. But the institute also has a history of questionable safety practices. The lab’s scientists reported a lack of appropriately trained technicians and investigators at the facility, prompting U.S. diplomatic scientists who visited in 2017 and 2018 [to alert](#) the State Department. At the same time, many scientists have pointed out, particularly in the aftermath of a recent, and [for some, contentious](#), examination of the lab leak hypothesis in [New York Magazine](#), that coronaviruses have typically been handled at BSL-2 or BSL-3 — lower security levels.

Such caveats aside, a prevailing theory among lab-leak proponents has been that SARS-CoV-2 was not simply brought into the Wuhan lab, but was somehow engineered there, given that many of its scientists routinely perform genetic research on coronaviruses and may also have “collaborated on publications and secret projects with China’s military,” according to a U.S. State Department [fact sheet](#) released during the last week of the Trump administration. On March 9, a Washington Post columnist, citing an unnamed State Department official, [suggested](#) that the Biden administration — while stopping well short of endorsing any particular theory regarding the origin of the virus — did not dispute many of the points made in that fact sheet.

Still, skeptics who doubt the lab leak hypothesis say SARS-CoV-2 doesn’t look anything like an engineered virus. Instead of appearing in discrete chunks, as would be expected with a genetically-engineered microbe, the differences with RaTg13 are distributed randomly throughout the viral genome. In an email to Undark, University of Chicago emeritus virology professor Bernard Roizman wrote that “we

are many, many years away from a complete understanding of viral gene functions and regulation — the key elements critical for construction of lethal viruses.”

The virus does have an inexplicable feature: a so-called “furin cleavage site” in the spike protein that helps SARS-CoV-2 pry its way into human cells. While such sites are present in some coronaviruses, they haven’t been found in any of SARS-CoV-2’s closest known relatives. “We don’t know where the furin site came from,” says Susan Weiss, a microbiologist who co-directs the Penn Center for Research on Coronaviruses and Other Emerging Pathogens at the University of Pennsylvania’s Perelman School of Medicine “It’s a mystery.” Although Weiss says SARS-CoV-2 is unlikely to have been engineered, she adds that the possibility that it escaped from a lab can’t be ruled out.

Reisman says it’s [also possible](#) that scientists working with undisclosed and even more closely related coronaviruses — perhaps one with a furin cleavage site and another with the SARS-CoV-2 gene backbone — may have been tempted to create a recombinant virus so they could study its properties. Indeed, researchers at the Wuhan Institute of Virology initially [failed to disclose](#) that eight other SARS-like coronaviruses had been detected in samples collected from the same mine cave where RaTG13 was found. Workers who cleaned bat feces in that cave, located in Yunnan Province near the border with Laos, went on to develop severe respiratory disease and one of them died.



Virologists working in the P4 lab of the Wuhan Institute of Virology in 2017, which many see as the likeliest site of a breakout. Credit: Feature China/Barcroft Media/Getty Images

Petrovsky leans towards another potential scenario, namely that SARS-CoV-2 might be evolved from coronaviruses that snuck into lab cultures. Related viruses in the same culture, he explains, such as one optimized for human ACE2 binding and another not, can swap genetic material to create new strains. “We’ve had this sort of thing happen in our own lab,” he says. “One day, you’re culturing flu, and then one day you sequence it, and you go ‘Holy shit, where did this other virus come from in our culture?’ Viruses are evolving the whole time and it’s easy for a virus to get into your culture without you knowing it.” Petrovsky and several co-authors speculated in a paper [published](#) as a non-peer-reviewed preprint in May of last year as to whether the virus was “completely natural” or whether it originated with “a recombination event that occurred inadvertently or intentionally in a laboratory handling coronaviruses.” The team wasn’t “saying this is a lab virus,” Petrovsky emphasizes, but rather “just presenting our data.”

But in late April 2020, as Petrovsky’s group was thinking about where to publish their work, “Trump blurted

out” that he had reason to believe that the virus came out of a Chinese lab, Petrovsky says. And at that point, he adds, much of “the left-wing media decided they were going to paint the whole lab thing as a conspiracy theory to bring down Trump.” When Petrovsky approached administrators of the preprint server bioRxiv, the paper was refused. BioRxiv staff replied that it would be more appropriately distributed after peer review, “which stunned us,” Petrovsky says. “We thought the whole point of preprint was to get important information out quickly.”

The paper was [subsequently posted](#) on a different preprint server called arXiv.org, based out of Cornell University. Soon reporters came calling, but most were from right-wing news outlets representing what Petrovsky calls “the Murdoch press.” Petrovsky says he had to work at stopping some tendentious reporters from distorting his paper’s findings to shape a narrative that SARS-CoV-2 had unequivocally been manufactured. And at the same time, he says, other media tried “to make a mockery of the whole possibility of the lab thing.”

Petrovsky describes himself as politically neutral, and according to sources, he is highly regarded in the vaccine world. Maria Elena Bottazzi, a microbiologist at Baylor College of Medicine, in Houston, says Petrovsky doesn’t make scientific claims that aren’t fully supported by evidence. And yet, simply following the science, Petrovsky suggests, had become too politically fraught. “We were dealing with global forces,” he says, “that are way more powerful than a scientist trying to tell a science-based story.”

Skeptics who doubt the lab leak hypothesis say SARS-CoV-2 doesn’t look anything like an engineered virus.

The Australian findings were also caught up in a backlash against papers claiming evidence of lab origins by scientists who had jumped opportunistically into the field. Many of these scientists had little relevant experience, and no understanding “of how molecular evolution actually works,” says Rasmus Nielsen, an evolutionary biologist and coronavirus expert at the University of California, Berkeley.

Nielsen cites as one example a Jan. 31 paper posted on bioRxiv by researchers from the Indian Institute of Technology, in New Delhi, that [suggested](#) there was an “uncanny similarity” between aspects of SARS-CoV-2 and HIV. In response to a deluge of criticism, the authors [withdrew the paper](#) only days after it had been posted. Because of the HIV manuscript and other poor-quality preprints, says Nielsen, the lab leak “became associated with these sorts of crackpot hypotheses and very, very, very shoddy science.”

In an email to Undark, John Inglis, a bioRxiv co-founder, acknowledged that “an extensive network of non-mainstream websites trafficking in theories about the man-made origin of the coronavirus” had amplified the HIV manuscript. From then on, any papers claiming a human-made origin for SARS-CoV-2 would be turned down, not as “a judgment of the investigations or their interpretations,” but “because such papers require peer review that only journals have the time and resources to do.”

By late spring of 2020, scientists in the natural origins camp had taken the upper hand in shaping opinions. Only a few researchers have looked deeply into SARS-CoV-2’s origins, and according to the Broad Institute’s Chan, the vast majority of those who did not investigate the question simply accepted

what they perceived to be the prevailing view. If scientists were unwilling to challenge the orthodoxy for fear of the consequences, Metzl adds, then that “made it hard for journalists to write credible stories about origins, particularly in the absence of evidence.”

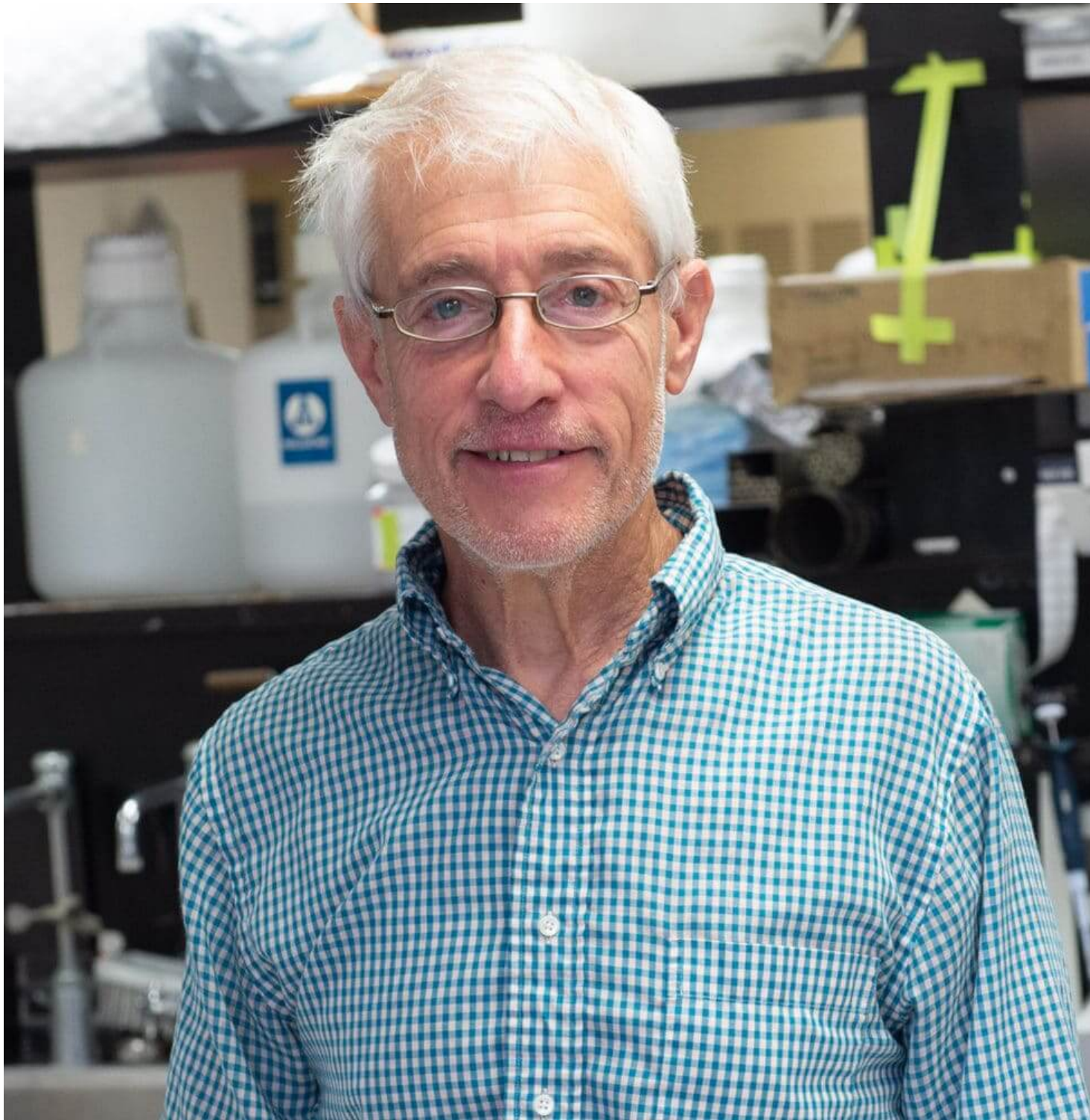
Perhaps no one played a greater role in galvanizing scientific opinions in support of natural origins than Peter Daszak, president of EcoHealth Alliance, a New York-based environmental health nonprofit. A long-time Wuhan Institute of Virology collaborator, Daszak — who in what many sources described as a conflict of interest was a member of the WHO-led team that visited China earlier this year — received grant funding from the National Institutes of Health to collaborate on research at the Chinese lab. (The Trump administration abruptly cut off this funding in April 2020 before it was [later reinstated with new restrictions](#).) Daszak is purported to have written a first draft of the Lancet statement condemning hypotheses other than natural origins as conspiracy theories. After repeated requests for an interview, the EcoHealth Alliance and Daszak declined to comment for this story.



Peter Daszak, a long-time collaborator with the Wuhan Institute of Virology, visits the Institute as a member of the WHO team investigating the origins of SARS-CoV-2. Daszak has pushed strongly against the possibility of a lab leak, and purportedly wrote the first draft of the Lancet statement. Credit: Hector Retamal/AFP/Getty Images

Stanley Perlman, a microbiologist and professor at the University of Iowa, in Iowa City, is listed as a co-author of the statement. In an email to Undark, he wrote that the “lab leak idea has several aspects, ranging from the statement that the virus was designed in a lab to ones that state the virus leaked from a laboratory but was not engineered.” The Lancet piece, he says, focused more on engineering, which

“would presumably be for a nefarious reason, but fortunately is impossible with our present knowledge.” The actual text of the Lancet statement, however, never makes this distinction.



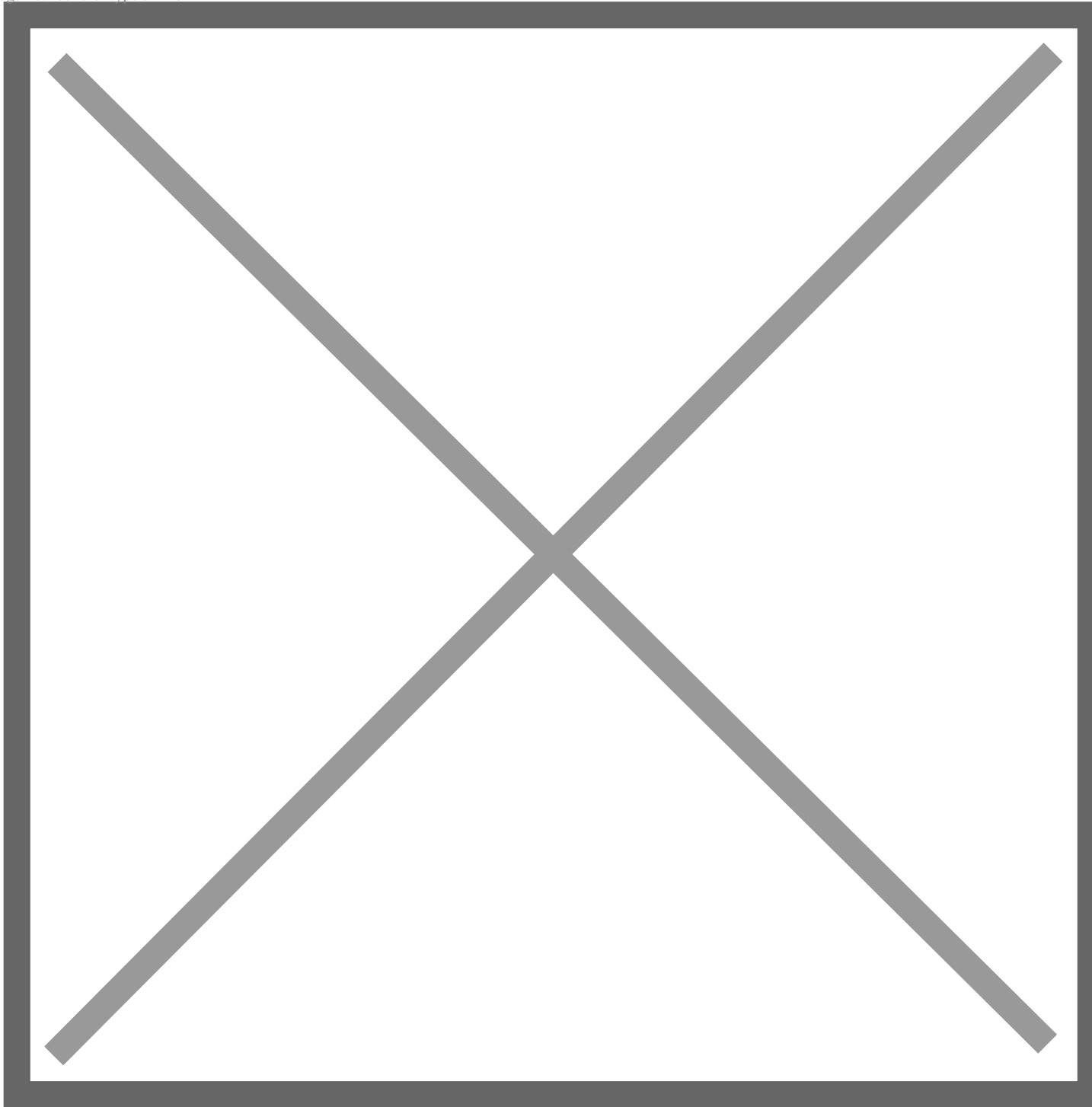
Microbiologist Stanley Perlman, a co-author of the Lancet statement, says the piece was focused on the idea that the virus could be engineered. Credit: Susan McClellan/UI Health Care

Charles Calisher, an emeritus professor in the Department of Microbiology, Immunology, and Pathology at Colorado State University, is also listed as a co-author. He says the conspiracy theory phrase was, in his opinion, over the top. “Unfortunately for me, [Daszak] listed everyone alphabetically and I was first,” he says. With his phone constantly ringing, Calisher says he told people he couldn’t say much until more information is available.

Relman agrees that in the absence of conclusive evidence, the message on origins should be “we don’t know.” After the Lancet statement, and then a [subsequent paper](#) on SARS-CoV-2’s origins written by scientists who concluded “we do not believe any type of laboratory-based scenario is plausible,” he found himself increasingly disheartened by those who he claimed had seized on a spillover scenario, despite “an amazing absence of data.” Relman says he felt he had to push back. So he wrote a widely-disseminated [opinion piece](#) in the Proceedings of the National Academy of Sciences claiming that a lab origin was among several potential scenarios; that conflicts of interest among those on all sides of the issue had to be revealed and addressed; and that uncovering SARS-CoV-2’s true origins was essential for preventing another pandemic. Efforts to investigate the origins, he wrote, “have become mired in politics, poorly supported assumptions and assertions, and incomplete information.”

One of the first media calls after the opinion piece was published came from Laura Ingraham at Fox News, Relman says. He declined the interview.

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Stanford microbiologist David Relman says a “fair and dispassionate discussion of the facts as we know them” was never a part of the lab-leak discussion. Credit: Alberto E. Rodriguez/Getty Images

When asked why he thought Daszak and others pushed so strongly against the possibility of a lab leak, Relman says they may have wanted to deflect perceptions of their work as endangering humankind. With

so-called “gain-of-function” experiments, for instance, scientists genetically manipulate viruses to probe their evolution — sometimes in ways that boost virulence or transmissibility. This sort of research can reveal targets for drugs and vaccines for viral diseases, including Covid-19, and was used at the Wuhan Institute of Virology in studies showing that certain bat coronaviruses were just a few mutations away from being able to bind to human ACE2. A [2015 paper](#) in Nature Medicine notes that the “potential to prepare for and mitigate future outbreaks must be weighed against the risk of creating more dangerous pathogens.”

Relman proposes that among those trying to suppress the lab-release hypothesis, there might have been “far too much protection of one’s self and one’s peers before allowing a really important question to receive a hearing.” And scientists collaborating with researchers in China, “might worry about their working relationship if they say anything other than ‘this threat comes from nature.’”

The lab leak “became associated with these sorts of crackpot hypotheses and very, very, very shoddy science,” says Nielsen.

Other scientists say opposition to the lab-leak hypothesis was grounded more in a general disbelief that SARS-CoV-2 could have been deliberately engineered. “This is what became politicized,” Perlman says. As to whether the virus may have escaped after evolving naturally, he says that is “more difficult to rule in or rule out.”

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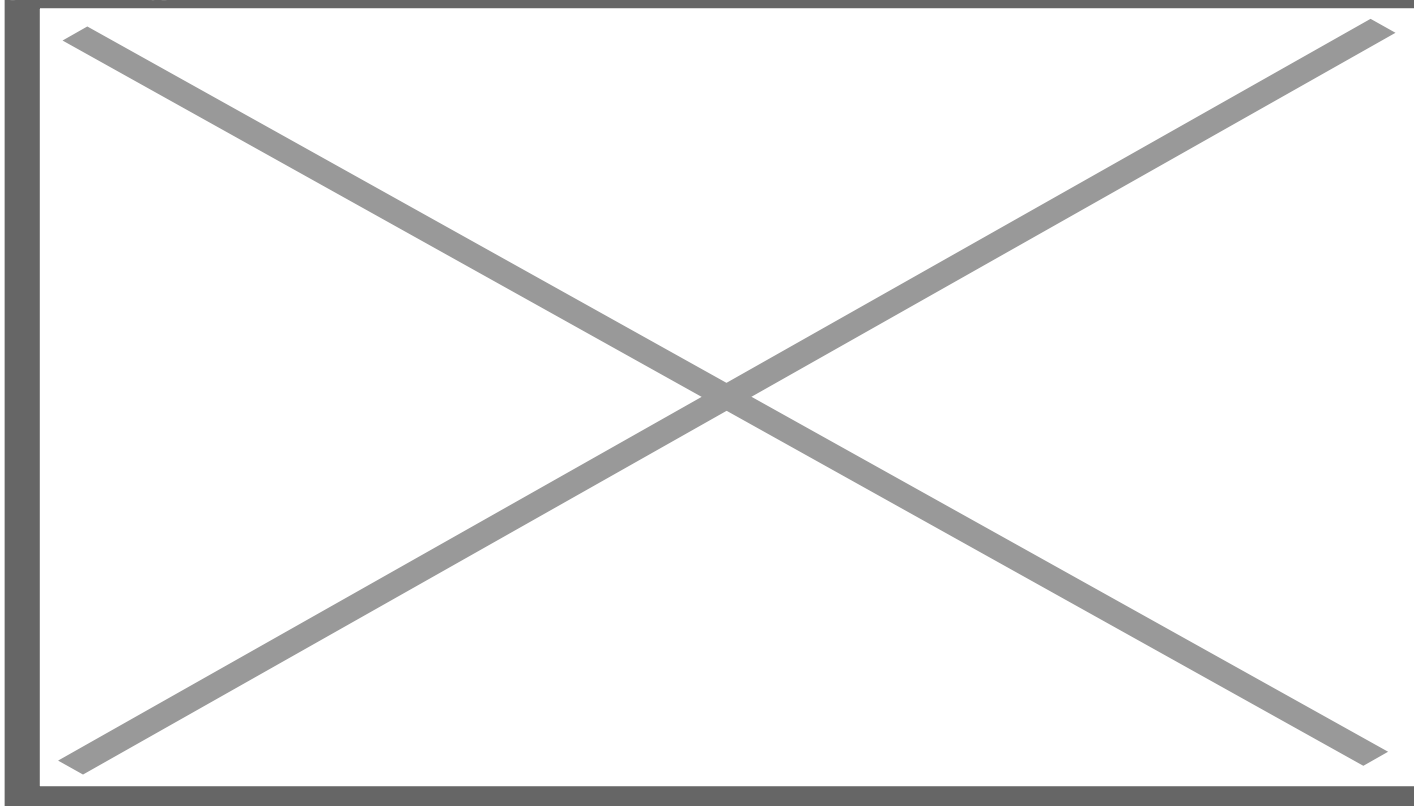
In an email message last week, Relman added that the question may never be fully settled. “From the natural spillover angle, it would take a confirmed contact between a proven naturally infected host species (e.g. bat) and a human or humans who can be shown with reliable, confirmed time-and-place details to have become infected as a result of the encounter, ahead of any other known human cases,” Relman says, “and then shown to have passed on the infection to others.” As for the lab-leak scenario, there would need to be “confirmed evidence of possession of the virus ahead of the first cases, and a likely mechanism for escape into humans” — all of which become less likely with the passage of time. “Finding the possible immediate parents of SARS-CoV-2 would help to understand the recent genomic/evolutionary history of the virus,” he adds, “but not necessarily how and where that history occurred.”

As it stands now, pandemic preparedness faces two simultaneous fronts. On the one hand, the world has experienced numerous pandemic and epidemic outbreaks in the last 20 years, including SARS, chikungunya, H1N1, Middle East Respiratory virus, several Ebola outbreaks, three outbreaks of norovirus, Zika, and now SARS-CoV-2. Speaking of coronaviruses, says Ralph Baric, an epidemiologist at the University of North Carolina, Chapel Hill, “it’s hard to imagine there aren’t variants” in bats with mortality rates approaching MERS’ 30 percent that also have “a transmissibility that is much more efficient. And that is terrifying.” Baric is emphatic that genetic research with viruses is essential to staying ahead of the

threat.

Yet according to Richard Ebright, a molecular biologist at Rutgers University, lab-release dangers are growing as well. The risk increases in proportion with the number of labs handling bioweapons and potential pandemic pathogens (more than 1,500 globally in 2010), he says, many of them, like the Wuhan lab, located in urban areas close to international airports. “The most dramatic expansion has occurred in China during the last four years — driven as an arms-race-style reaction to biodefense expansion in the U.S., Europe, and Japan,” Ebright wrote in an email to Undark. “China opened two new BSL-4 facilities, in Wuhan and in Harbin, in the last four years,” he added, “and has announced plans to establish a network of hundreds of new BSL-3 and BSL-4 labs.”

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The BSL-4 laboratory on the campus of the Wuhan Institute of Virology. As the number of labs handling dangerous pathogens grows, so too does the risk of lab-release dangers. Credit: Hector Retamal/AFP/Getty Images

Meanwhile, squabbles over SARS-CoV-2’s origins continue, some of them heated. During a recent exchange on Twitter, Chan was compared to a QAnon supporter and an insurrectionist. A few months prior, she had tweeted about issues of research integrity and stated that if the actions of scientists and journal editors were to obscure the origins of the virus, then those individuals would be complicit in the deaths of millions of people. (Chan has since deleted that tweet, which she says she regrets posting.)

“Tempers are high,” Nielsen says, making it hard for qualified scientists to have any sort of serious discussion.

In Australia, Petrovsky says he is trying to stay above the fray. He says he was warned to avoid speaking publicly about his modeling findings. “A lot of people advised us ‘even if it’s good science, don’t talk about it. It will have a negative impact on your vaccine development. You will get attacked; they will try to discredit you.’” But in the end, that’s not what happened, says Petrovsky. Last year, amid the origins debate, his team became the first in the Southern Hemisphere to take a vaccine for Covid-19 into human clinical trials.

“If we are at the point where all science is politicized and no one cares about truth and only being politically correct,” he says, “we may as well give up and shut down and stop doing science.”

Charles Schmidt is a recipient of the National Association of Science Writers’ Science in Society Journalism Award. His work has appeared in Science, Nature Biotechnology, Scientific American, Discover Magazine, and The Washington Post, among other publications. Find Charles at his website <http://www.schmidtwriting.com>.

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