

PANDEMIC TECHNOLOGY PROJECT

# Inside the risky bat-virus engineering that links America to Wuhan

China emulated US techniques to construct novel coronaviruses in unsafe conditions.

By Rowan Jacobsen

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MS TECH | AP

In 2013, the American virologist Ralph Baric approached Zhengli Shi at a meeting. Baric was a top expert in coronaviruses, with hundreds of papers to his credit, and Shi, along with her team at the Wuhan Institute of Virology, had been discovering them by the fistful in bat caves.

In one sample of bat guano, Shi had detected the genome of a new virus, called SHC014, that was one of the two closest relatives to the original SARS virus, but her team had not been able to culture it in the lab.

Baric had developed a way around that problem—a technique for “reverse genetics” in coronaviruses. Not only did it allow him to bring an actual virus to life from its genetic code, but he could mix and match parts of multiple viruses. He wanted to take the “spike” gene from SHC014 and move it into a genetic copy of the SARS virus he already had in his lab. The spike molecule is what lets a coronavirus open a cell and get inside it. The resulting chimera would demonstrate whether the spike of SHC014 would attach to human cells.

If it could, then it could help him with his long-term project of developing universal drugs and vaccines against the full spectrum of SARS-like viruses that he increasingly considered sources of potential pandemics. A SARS vaccine had been developed, but it wasn’t expected to be very effective against related coronaviruses, just as flu shots rarely work against new strains. To develop a universal vaccine that will elicit an antibody response against a gamut of SARS-like viruses, you need to show the immune system a cocktail of spikes. SHC014 could be one of them.

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## If you study a hundred different bat viruses, your luck may run out.

-Ralph Baric, University of North Carolina

Baric asked Shi if he could have the genetic data for SHC014. “She was gracious enough to send us those sequences almost immediately,” he says. His team introduced the virus modified with that code into mice and into a petri dish of human airway cells. Sure enough, the chimera exhibited “robust replication” in the human cells—evidence that nature was full of coronaviruses ready to leap directly to people.

While Baric’s study was in progress, the National Institutes of Health announced that it would temporarily halt funding for “gain of function” research—experiments that make already dangerous viruses more virulent or transmissible—on SARS, MERS (which is also caused by a coronavirus), and influenza until the safety of such research could be assessed. The announcement brought Baric’s work to a standstill.

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Baric was a legend in the field, but no matter how many safety precautions are taken, there is always a chance that a never-before-seen virus can escape and trigger an outbreak. Baric felt that the extreme measures he took in the lab minimized the risk, and in fact made his work categorically different from the high-risk influenza work the NIH had been targeting. He also felt that his research was urgent: new cases of MERS, spread by camels, were even then popping up in the Middle East. Eventually the NIH agreed, waving him forward.



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During a hearing on May 11, 2021, Senator Rand Paul confronted Anthony Fauci over funding of bat-virus research by the National Institutes of Health.

GREG NASH/POOL VIA AP

His 2015 paper, “A SARS-like cluster of circulating bat coronaviruses shows potential for human emergence,” was a tour de force, utilizing bleeding-edge genetic technology to alert the civilized world to a looming danger on its periphery. It also revived concerns about gain-of-function experiments, which Baric had known it would. In the paper, he spelled out the extra precautions he'd taken and held up the research as a test case. “The potential to prepare for and mitigate future outbreaks must be weighed against the risk of creating more dangerous pathogens,” he wrote. “Scientific review panels may deem similar studies building chimeric viruses based on circulating strains too risky to pursue.”

The NIH decided the risk was worth it. In a potentially fateful decision, it funded work similar to Baric's at the Wuhan Institute of Virology, which soon used its own reverse-genetics technology to make numerous coronavirus chimeras.

Unnoticed by most, however, was a key difference that significantly shifted the risk calculation. The Chinese work was carried out at biosafety level 2 (BSL-2), a much lower tier than Baric's BSL-3+.

What caused the covid-19 pandemic remains uncertain, and Shi says her lab never encountered the SARS-CoV-2 virus before the Wuhan outbreak. But now that US officials have said the possibility of a lab accident needs to be investigated, the spotlight has fallen on American funding of the Wuhan lab's less safe research. Today a chorus of scientists, including Baric, are coming forward to say this was a misstep. Even if there is no link to covid-19, allowing work on potentially dangerous bat viruses at BSL-2 is “an actual scandal,” says Michael Lin, a bioengineer at Stanford University.

The simmering concern that the US funded risky research in China burst into the national discussion on May 11, when Senator Rand Paul accused Anthony Fauci, the longtime director of the NIH's National Institute of Allergy and Infectious Diseases, of funding “supervirus” research in the US and “making a huge mistake” by trading the know-how to China. Paul repeatedly confronted Fauci and demanded to know if he had funded gain-of-function research in that country. Fauci denied the accusation, stating categorically: “The NIH has not ever, and does not now, fund gain-of-function research in the Wuhan Institute of Virology.”

During a hearing on May 11, 2021, Senator Rand Paul confronted Anthony Fauci over funding of bat-virus research by the National Institutes of Health.

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The denial rests on the NIH's specific definition of what was covered by the moratorium: work that would have deliberately enhanced SARS-like viruses, MERS, or flu by—for example—making them easier to spread through the air. The Chinese research did not have the specific goal of making the viruses more deadly, and rather than SARS itself, it used SARS's close cousins, whose real-world risk to humans was unknown—in fact, determining the risk was the point of the research. Just as when you trade in part of a poker hand for fresh cards, there was no way of knowing whether the final chimeras would be stronger or weaker.

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The NIH has still not fully explained its decision-making and did not reply to questions. Citing a pending investigation, it has declined to release copies of the grant that sent the Wuhan institute about \$600,000 between 2014 and 2019. It has also revealed little about its new [system](#) for assessing gain-of-function risks, which is carried out by an anonymous review panel whose deliberations are not made public. Until there's more sunlight, the agency will be fighting speculation, from Paul and others, that what occurred is a scenario Fauci himself had outlined in [a 2012 commentary](#) discussing research on pandemic germs.

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**“The only impact of this work is the creation, in a lab, of a new, non-natural risk.”**

Richard Ebright, Rutgers University

“Consider this hypothetical scenario,” Fauci wrote. “An important gain-of-function experiment involving a virus with serious pandemic potential is performed in a well-regulated, world-class laboratory by experienced investigators, but the information from the experiment is then used by another scientist who does not have the same training and facilities and is not subject to the same regulations. In an unlikely but conceivable turn of events, what if that scientist becomes infected with the virus, which leads to an outbreak and ultimately triggers a pandemic?”

### A wake-up call

Paul's grilling of Fauci brought new scrutiny to the relationship between Ralph Baric's lab at UNC and Zhengli Shi's at WIV, with some narratives painting Baric as the Sith master of SARS and Shi as his ascendant apprentice. They did share resources—for example, Baric sent the transgenic mice with human lung receptors to Wuhan. But after their initial collaboration, the two centers were more like competitors. They were in a race to identify dangerous coronaviruses, assess the potential threat, and develop countermeasures like vaccines.

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For Baric, that research started in the late 1990s. Coronaviruses were then considered low risk, but Baric's

studies on the genetics that allowed viruses to enter human cells convinced him that some might be just a few mutations away from jumping the species barrier.

That hunch was confirmed in 2002–’03, when SARS broke out in southern China, infecting 8,000 people. As bad as that was, Baric says, we dodged a bullet with SARS. The disease didn’t spread from one person to another until about a day after severe symptoms began to appear, making it easier to corral through quarantines and contact tracing. Only 774 people died in that outbreak, but if it had been transmitted as easily as SARS-CoV-2, “we would have had a pandemic with a 10% mortality rate,” Baric says. “That’s how close humanity came.”

As tempting as it was to write off SARS as a one-time event, in 2012 MERS emerged and began infecting people in the Middle East. “For me personally, that was a wake-up call that the animal reservoirs must have many, many more strains that are poised for cross-species movement,” says Baric.

By then, examples of such dangers were already being discovered by Shi’s team, which had spent years sampling bats in southern China to locate the origin of SARS. The project was part of a global viral surveillance effort spearheaded by the US nonprofit EcoHealth Alliance. The nonprofit—which has an annual income of over \$16 million, more than 90% from government grants—has its office in New York but partners with local

research groups in other countries to do field and lab work. The WIV was its crown jewel, and Peter Daszak, president of EcoHealth Alliance, has been a coauthor with Shi on most of her key papers.

By taking thousands of samples from guano, fecal swabs, and bat tissue, and searching those samples for genetic sequences similar to SARS, Shi’s team began to discover many closely related viruses. In a cave in Yunnan Province in 2011 or 2012, they discovered the two closest, which they named WIV1 and SHC014.

Shi managed to culture WIV1 in her lab from a fecal sample and show that it could directly infect human cells, proving that SARS-like viruses ready to leap straight from bats to humans already lurked in the natural world. This showed, Daszak and Shi argued, that bat coronaviruses were a “substantial global threat.” Scientists, they said, needed to find them, and study them, before they found us.

Many of the other viruses couldn’t be grown, but Baric’s system provided a way to rapidly test their spikes by engineering them into similar viruses. When the chimera he made using SHC014 proved able to infect human cells in a dish, Daszak told the press that these revelations should “move this virus from a candidate emerging pathogen to a clear and present danger.”

To others, it was the perfect example of the unnecessary dangers of gain-of-function science. “The only impact of this work is the creation, in a lab, of a new, non-natural risk,” the Rutgers microbiologist Richard Ebright, a longtime critic of such research, told Nature.

To Baric, the situation was more nuanced. Although his creation might be more dangerous than the original mouse-adapted virus he’d used as a backbone, it was still wimpy compared with SARS—certainly not the supervirus Senator Paul would later suggest.

In the end, the NIH clampdown never had teeth. It included a clause granting exceptions “if head of funding agency determines research is urgently necessary to protect public health or national security.” Not only were Baric’s studies allowed to move forward, but so were all studies that applied for exemptions. The funding restrictions were lifted in 2017 and replaced with a more lenient system.

## Tyvek suits and respirators

If the NIH was looking for a scientist to make regulators comfortable with gain-of-function research, Baric was the obvious choice. For years he’d insisted on extra safety steps, and he took pains to point these out in his 2015 paper, as if modeling the way forward.

The [CDC recognizes](#) four levels of biosafety and recommends which pathogens should be studied at which level. Biosafety level 1 is for nonhazardous organisms and requires virtually no precautions: wear a lab coat and gloves as needed. BSL-2 is for moderately hazardous pathogens that are already endemic in the area, and relatively mild interventions are indicated: close the door, wear eye protection, dispose of waste materials in an autoclave. BSL-3 is where things get serious. It’s for pathogens that can cause serious disease through respiratory transmission, such as influenza and SARS, and



## **Top researchers are calling for a real investigation into the origin of covid-19**

A group of prominent biologists say there needs to be a “safe space” for asking whether the coronavirus came out of a lab.

the associated protocols include multiple barriers to escape. Labs are walled off by two sets of self-closing, locking doors; air is filtered; personnel use full PPE and N95 masks and are under medical surveillance. BSL-4 is for the baddest of the baddies, such as Ebola and Marburg: full moon suits and dedicated air systems are added to the arsenal.

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“There are no enforceable standards of what you should and shouldn’t do. It’s up to the individual countries, institutions, and scientists.”

Filippa Lentzos, King’s College London

In Baric’s lab, the chimeras were studied at BSL-3, enhanced with additional steps like Tyvek suits, double gloves, and powered-air respirators for all workers. Local first-responder teams participated in regular drills to increase their familiarity with the lab. All workers were monitored for infections, and local hospitals had procedures in place to handle incoming scientists. It was probably one of the safest BSL-3 facilities in the world. That still wasn’t enough to prevent a handful of errors over the years: some scientists were even bitten by virus-carrying mice. But no infections resulted.

### Brand-new pathogens

In 2014, the NIH awarded a five-year, \$3.75 million grant to EcoHealth Alliance to study the risk that more bat-borne coronaviruses would emerge in China, using the same kind of techniques Baric had pioneered. Some of that work was to be subcontracted to the Wuhan Institute of Virology.

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Two years later, Daszak and Shi published a paper reporting how the Chinese lab had engineered different versions of WIV1 and tested their infectiousness in human cells. The paper announced that the WIV had developed its own reverse-genetics system, following the Americans’ lead. It also included a troubling detail: the work, which was funded in part by the NIH grant, had been done in a BSL-2 lab. That meant the same viruses that Daszak was holding up as a clear and present danger to the world were being studied under conditions that, according to Richard Ebright, matched “the biosafety level of a US dentist’s office.”

Ebright believes one factor at play was the cost and inconvenience of working in high-containment conditions. The Chinese lab’s decision to work at BSL-2, he says, would have “effectively increas[ed] rates of progress, all else being equal, by a factor of 10 to 20”—a huge edge.

Work at the WIV was indeed progressing quickly. In 2017, Daszak and Shi followed with another study, also at BSL-2, that one-upped Baric’s work in North Carolina. The WIV had continued to unearth dozens of new SARS-like coronaviruses in bat caves, and it reported making chimeras with eight of them by fusing the spikes of the new viruses to the chassis of WIV1. Two of them replicated well in human cells. They were, for all intents and purposes, brand-new pathogens.

The revelation that the WIV was working with SARS-like viruses in subpar safety conditions has led some people to reassess the chance that SARS-CoV-2 could have emerged from some type of laboratory incident. “That’s screwed up,” the Columbia University virologist Ian Lipkin, who coauthored the seminal paper arguing

that covid must have had a natural origin, told the journalist Donald McNeil Jr. “It shouldn’t have happened. People should not be looking at bat viruses in BSL-2 labs. My view has changed.”

But the WIV was not breaking any rules by working at BSL-2, says Filippa Lentzos, a biosecurity expert at King’s College London “There are no enforceable standards of what you should and shouldn’t do. It’s up to the individual countries, institutions, and scientists.” And in China, she says, the vertiginous rise of high-tech biological research has not been accompanied by an equivalent increase in oversight.

In an email, Zhengli Shi said she followed Chinese rules that are similar to those in the US. Safety requirements are based on what virus you are

studying. Since bat viruses like WIV1 haven't been confirmed to cause disease in human beings, her biosafety committee recommended BSL-2 for engineering them and testing them and BSL-3 for any animal experiments.

In response to questions about the decision to do the research in BSL-2 conditions, Peter Daszak forwarded a statement from EcoHealth Alliance stating that the organization "must follow the local laws of the countries in which we work" and that the NIH had determined the research was "not gain-of-function."

## Questioning China

There is no law against using tighter lab security, however, and according to Baric, these viruses deserve it. "I would never argue that WIV1 or SHC014 should be studied at BSL-2, because they can grow in primary human cells," he says. "There's some risk associated with those viruses. We have no idea whether they could actually cause severe disease in a human, but you want to err on the side of caution ... If you study a hundred different bat viruses, your luck may run out."

Since the pandemic began, Baric has not said much about the possible origins of the virus or about his Chinese counterparts. On several occasions, however, he has quietly pointed to safety concerns at the WIV. In May 2020, when few scientists were willing to consider a lab leak in public, he published [a paper](#) acknowledging that "speculation about accidental laboratory escape will likely persist, given the large collections of bat virome samples stored in labs in the Wuhan Institute of Virology, the facility's proximity to the early outbreak, and the operating procedures at the facility." He flagged [Daszak and Shi's BSL-2 paper](#), in case anyone didn't understand what he was saying.

Ralph Baric of the University of North Carolina specializes in the genetic engineering of coronaviruses as part of vaccine and drug research.

COURTESY PHOTO

The National Institutes of Health has also revisited its ties to the Wuhan lab. In April of 2020, the NIH terminated its grant to EcoHealth Alliance for bat virus research. In a [follow-up letter](#) to Daszak on July 8, it offered to reinstate the grant, but only if EcoHealth Alliance could allay its concerns, noting reports that the WIV "has been conducting research at its facilities in China that pose serious bio-safety concerns" for other countries. It added, "We have concerns that WIV has not satisfied safety requirements under the award, and that EcoHealth Alliance has not satisfied its obligations to monitor the activities of its subrecipient."

The genetic code of SARS-CoV-2 does not resemble that of any virus the WIV was known to be culturing in its lab, such as WIV1, and Baric says he still believes a natural spillover is the most likely cause. But he also knows the intricate risks of the work well enough to see a possible path to trouble. That is why, in May of this year, he joined 17 other scientists in a letter in the journal *Science* calling for a thorough investigation of his onetime collaborator's lab and its practices. He wants to know what barriers were in place to keep a pathogen from slipping out into Wuhan's population of 13 million, and possibly to the world.

"Let's face it: there are going to be unknown viruses in guano, or oral swabs, which are oftentimes pooled. And if you're attempting to culture a virus, you're going to have novel strains being dropped onto culture cells," Baric says. "Some will grow. You could get recombinants that are unique. And if that was being done at BSL-2, then there are questions you want to ask."

by Rowan Jacobsen

