Meet Resista

▶ Yaoxing Huang, David Ho, and Sho Iketani

Renowned researcher David Ho is leading a team of aggressive young scientists racing to beat the coronavirus

By Robert Langreth and Susan Berfield
Photographs by Samantha Casolari

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It seems obvious now that David Ho, arguably the world's most famous AIDS researcher, would get involved in seeking a treatment for Covid-19, the disease caused by the new coronavirus. It seems obvious that he would redirect the work of his several dozen scientists at the Aaron Diamond AIDS Research Center. That he would, as he says, "rob Peter to pay Paul" to get started with funds meant for the lab's HIV studies. That he would receive $2.1 million from the Jack Ma Foundation in Hangzhou, China, without even asking and an additional $6 million from other private donors, among them a few very concerned businesspeople.

But in late December, when Ho was tracking reports of a few cases of unexplained pneumonia in Wuhan, it wasn't obvious he'd be needed. "We were paying attention but didn't think we would get involved. It seemed rare—and over there," he says. In early January, as his lab changed its affiliation from Rockefeller University to Columbia University and moved to Upper Manhattan, the situation in Wuhan had become worse. Ho still wasn't sure if he should get involved. "The scientists in China were already doing so much," he says. Many of those scientists, in Beijing, Hong Kong, and Shanghai, are former students of his. "They could very well do the job."

He'd also seen funders lose interest in emerging diseases after the immediate panic about an outbreak subsided. Severe acute respiratory syndrome, or SARS, for example, had been contained relatively quickly in 2002, and as soon as it was, money for research became scarce. Ho's lab had developed antibodies that could have been used to pursue treatments for SARS, another coronavirus, but it was too late—he couldn't raise the $20 million or so he needed to continue pressing forward on his own. "No one seemed to care," he says. "That's frustrating." If he'd found the money, it's possible he'd be closer to a treatment for the new coronavirus.

By mid-January the magnitude of this epidemic was becoming clear. The Chinese government was making plans to quarantine the city of Wuhan, and four other countries reported cases. Scientists had identified the virus and shared its gene sequence. Ho also believed that this time the Chinese government, for one, would provide funding for sustained research. "They've learned their lesson," he says. He decided to get involved.

Eight weeks later, the virus has taken hold around the world. Counting the ill and calculating the rates of infection and death are daily, hourly exercises in caution and dread. The 1918 flu pandemic killed at least 50 million people. The HIV pandemic has so far infected 75 million and killed 32 million. The death rate for Covid-19 appears to be much lower—it remains uncertain—but the illness spreads easily. If it reaches only 1% of the global population, that would mean 75 million people would be infected, and at the current mortality rates, 1 million would die.

Scientists at Ho's lab, and at Johnson & Johnson, Pfizer, Regeneron, and at least 10 other drug and biotech companies, are working as quickly as they can to identify treatments. This virus is part of a family they've come to know. They're rushing to test old compounds even as they devise programs to create new ones. Among the furthest along is Gilead Sciences Inc., which is testing remdesivir, an antiviral drug tried on Ebola ▶

◀ patients, on coronavirus patients around the world. Gilead expects to report initial results in April.

Scientists say they can tame this coronavirus, but for a while it will move faster than they'll be able to. It may be a year or more before any specific treatment for Covid-19 is available. Until then we'll have to contain it with distance and soap and the drugs we already have.

Even once there's a treatment, it's probable that Covid-19 will remain with us for longer than we'd like. Completely wiping out something this widespread is exceedingly difficult, Ho is quick to say. Only one such virus has been eradicated: smallpox. That took about 20 years.

On an early March morning, before New York City began closing down, Ho took some time to talk about the work under way at his lab. He wore a suit, and though he seemed perfectly comfortable, he'd normally be in jeans. He'd be busy, but his phone wouldn't be constantly ringing. He wouldn't be meeting with university trustees, or advising the NBA, or conferring with the head of China's center for disease control and prevention, or appearing on the *Rachel Maddow Show*. He'd be expecting his staff to have unpacked their moving boxes.

But this isn't a normal time for anyone, and especially not for a scientist such as Ho. He was among the first to champion a powerful combination of drugs to attack HIV and to push for them to be administered early instead of after a patient developed symptoms. It was an unconventional approach that became the standard of care and helps explain why HIV is a chronic disease but not necessarily a deadly one. It also explains why Ho was the first doctor to be named *Time* magazine's Man of the Year, in 1996, and five years later was awarded the Presidential Citizens Medal. The plaque hangs on the wall behind his desk.

Ho is 67 years old, measured and focused, and central to a network of former colleagues and students who've known that a moment like this was coming: a pandemic that could be the biggest viral threat to humanity since HIV emerged in the 1980s.

Ho has developed an ambitious and expedited effort to come up with coronavirus drugs. The early stages of drug development typically take from five to 10 years, but he thinks it's possible to have the most promising compounds ready for animal testing in only one. His hope is to create a single pill that could treat this coronavirus and the ones that will come after. "Surely there will be another one," he says. "This is the third outbreak in two decades." SARS started in China and eventually killed almost 800 people; Middle East respiratory syndrome emerged in 2012 and has killed more than 850 in sporadic outbreaks since then.

"We're reading strange literature about bat research," Ho says. "Bats account for one-fifth of the mammals on this planet. That's trivia we didn't know. There are so many viruses that reside in bats—SARS and Ebola and perhaps this coronavirus." Covid-19 isn't the first, and it won't be the last. Ho wants to prepare for the next one now.

Hearing that was good enough for Jack Ma, the richest man in Asia. And it was sufficient for Zhi Hong, chief executive officer of Brii Biosciences, to also put in $2 million. Hong had been an infectious disease expert at GlaxoSmithKline Plc and has known Ho for years. "David has put together a quick but very reasonable program," Hong says. If Ho's lab comes up with a drug, a big pharmaceutical company would have to come in to test and produce it. There's no formal agreement yet about how that would happen. There was no time for lawyers. "Right now we're just investing in faith and trust in the relationship and David's reputation," Hong says. "We just said, 'Take the money.' "

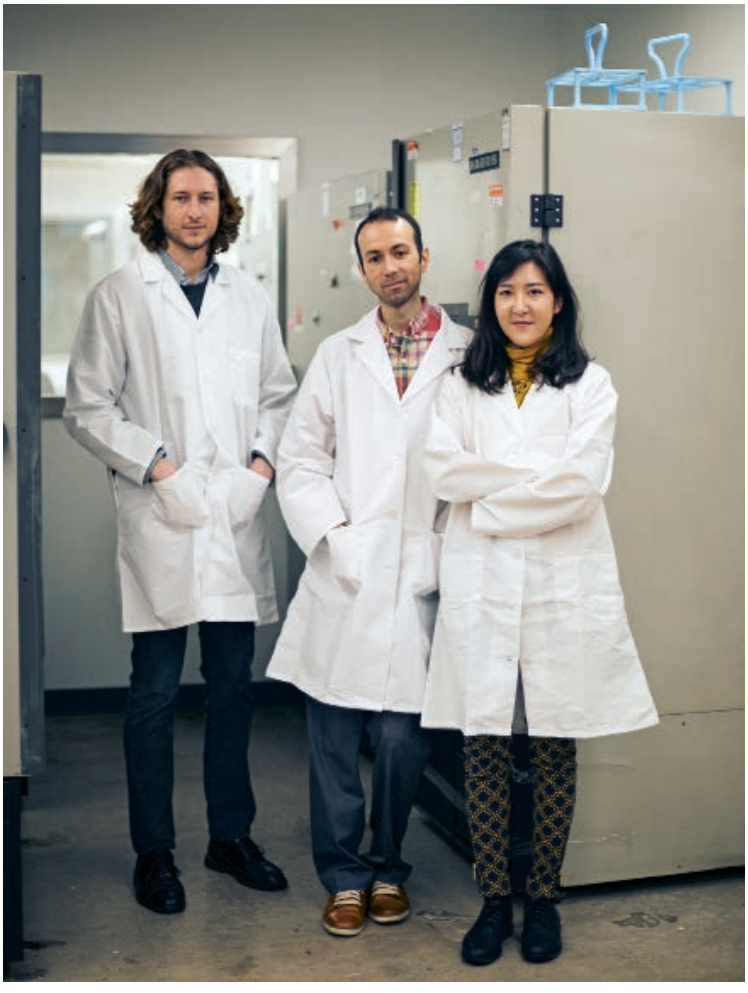
The most straightforward of the lab's projects aims to find an antibody to block the virus from entering cells, either to prevent infection or to treat it. The first step was getting hold of specific white blood cells, called memory B cells, from patients who have recovered from Covid-19. These cells, named because they can remember a virus for decades, contain markers on their surfaces that allow the body to rapidly generate many antibodies to that virus. These antibodies help protect against Covid-19 infection. In late January, Ho called on his connections in Hong Kong to take blood samples from two convalescent patients. His New York staff spent days getting permission from the governments and arranging the shipping. The cells were purified, placed in tiny vials, frozen in liquid nitrogen at -150C, and sent to Ho's lab by a specialized courier service. They arrived intact in late February.

As soon as they received the cells, Ho's lab went to work sorting out the B cells, extracting RNA, making DNA for numerous anti-coronavirus antibodies, and expressing those antibodies on the surface of yeast cells. "Then we go fishing," Ho says. "And we come with bait." The bait is the spike proteins that protrude from the surface of the virus—or, in this instance, the lab-created pseudo virus. The tighter an antibody binds to the protein, the better. "We pull out many, compare activity, and select the best," he says. "We could then change parts of the antibody to make it fit even tighter."

The chances that this research, or similar research elsewhere, will yield a treatment are relatively high. The strategy worked for Ebola. Regeneron Pharmaceuticals Inc., which developed a successful Ebola antibody treatment, is also working on a coronavirus antibody "cocktail" and says human trials could begin by early summer. But any such drug would have to be injected, which would likely require it to be refrigerated and administered by doctors—all of which would limit its use. It's not the ideal. But it's what might be good enough as a start.

Ho's early HIV research focused on a crucial enzyme called protease, which acts as a kind of molecular scissors, cutting up viral proteins to help them replicate. One key set of drugs he tested on HIV patients in the 1990s were protease inhibitors: They interrupted that stage of the viral life cycle in an infected patient. He's hoping to identify potential coronavirus protease inhibitors, which would act in much the same way. "Even if the protease is different, there are enough similarities to apply our knowledge and the chemistry," he says.

▼Alejandro Chavez, center, with doctoral students Samuel Resnick and Debbie Hong



Alejandro Chavez, an assistant professor of pathology and biology at Columbia, is helping Ho in this part of the research. Traditional labs at pharmaceutical companies test potential drug compounds on one viral strain at a time. Chavez has devised a radically different screening system that allows him to simultaneously test compounds on dozens—and if successful, find the ones that will work not only on Covid-19 but on other coronaviruses as well.

Chavez, 37, runs his own lab at Columbia, located across the street from Ho's. He packs bundles of information into every sentence without pause. He's animated and energized by the moment. His office is small, his desk crowded with papers and a huge jar of cheap candy. Perched on a ledge behind his desk is an award from his fellow residents at Massachusetts General Hospital: The "'Yo dude I have this crazy idea let me explain it to you in one long stream-of-consciousness email' award for exuberant scientific creativity."

In January, Chavez and Debbie Hong, one of the doctoral students working in his lab, were reading about the coronavirus like everyone else. When its genome was posted on a public-health website, they downloaded the sequence, found the protease gene, and paid a bioscience company about $80 to synthesize it.

Soon after, they got a call from Ho. "Ho nucleated a team," Chavez says. Nucleated? "Yeah, he nucleated a team." He means one of Hong's thesis advisers at Columbia, Stephen Goff, decided to combine his research efforts with Ho's. Then, because he knew Ho was still looking for university scientists to join his effort, Goff told him, "There's these crazy people—maybe we should bring them in." That was Chavez, Hong, and a few others in the lab. Ho was impressed by how rapidly they could screen the molecules that might inhibit all kinds of coronavirus protease enzymes; his search could be accelerated beyond what he could do on his own. "He wants to push it forward at warp speed," Chavez says.

Chavez starts to explain his method. Then stops. Then starts. He's applied for a patent and isn't sure how much he wants to reveal. "I've never tried to explain this to a layperson and obfuscate at the same time," he says. "I've only ever presented this once. I've been trying to stay stealth. OK, I'll just disclose it." One of the problems with screening drugs against more than one viral protease at a time is that it's hard to tell which drugs are blocking which proteases. Chavez solved this problem by putting proteases from each virus into different cells, then creating what he calls nametags for each of the cells. He adds possible drug compounds to the cells and uses genome sequencing to read the tags, which allows him to see whether any of the viral proteases are blocked by each drug. "I look at how abundant each of the nametags are—'How are you doing, Bob, John?'—and I see if the protease is on or off. If it's off, then that compound inhibited it. If the protease is on, then that compound didn't do anything."

Chavez is speaking hypothetically. He's still working out the controls. "We're not insane. We're going to be very methodical," he says. "So if I put in a compound that I know its activity, do I see that activity? Do I see that activity over four days? Does every single day give me the right answer? Does the answer ever change? Do I see things I know shouldn't happen?"

Chavez expects to begin testing the actual compounds in early April. In the meantime, "we've been busy collecting those compounds from chemical libraries," Ho says. He was able to obtain a curated selection of potential protease-inhibiting molecules from a research company in Shanghai called WuXi AppTec Co. The founder is a friend of Ho's who received his doctorate in chemistry from Columbia. It's likely that if someone other than Ho had asked, the compounds, as crucial as they may turn out to be, would have remained in China.

It might take three to six months for Chavez to detect a few lead compounds that efficiently block coronavirus proteases. If—when—he does, Ho will connect him to chemists who will, over a matter of a few more months, increase the potency of the compounds by 100%, maybe 1,000%. "We know that kind of gain is doable," Ho says. It would be an important but still early step in creating a drug that would stop not only one viral protease but proteases from many coronaviruses. Because now we all know they're out there. Ⓑ