ENDPOINTS NEWS

Inside the quixotic 30-year quest that gave us the Covid-19 treatments, vaccines and could unlock vaccinology's new holy grail

by **Jason Mast** on August 25th, 2021

John Mascola, America's soft-spoken, no-nonsense chief vaccinologist, spent 2020 on the fourth floor of the Vaccine Research Center in Bethesda, MD, primarily working on three projects. There's a decent chance one of them has already been injected in your arm — twice. Another was infused into hundreds of thousands of Covid-19 patients, potentially protecting them from hospitalization.

And the third is a scientific codex that has bedeviled Mascola, his colleagues, and researchers around the world for the better part of three decades.

Before Covid-19, the largest and longest-running mystery in infectious disease was how to build a vaccine against HIV, the famously evasive virus that has claimed the lives of 36 million people since the 1980s. Within a year of the novel coronavirus' discovery, two vaccines were already available and shown to be 95% effective. Thirty-eight years after HIV's discovery, you could fill encyclopedias with all scientists have learned about the pathogen, but it's hard to say whether or not we're any closer to a vaccine.

Part of that disparity has to do with the coronavirus' comparative simplicity — "this is a stupid easy virus to vaccinate against," as the immunologist Michael Farzan put it last year. HIV is, by any definition, the hardest.

But part of it also has to do with all the tools researchers developed trying to inoculate against HIV. Confronted by a microbial enemy more cunning than any humanity had ever encountered, the world's leading researchers were forced to go back to the drawing board. Crossing disciplines and continents, they came up with new tools to understand both viruses and the immune system and new ways of turning that knowledge into walls and weapons against any pathogen, however stupid or ingenious it may be.

Those same researchers jumped out in the winter of 2020 to study the coronavirus, unleashing tools honed on a far more cunning foe. Mascola, who had spent thirty years on HIV vaccine development, most notably launched the effort to find the first antibody treatment, later marketed by Eli Lilly. Legendary AIDS researcher David Ho worked on his own antibody treatment and conducted crucial studies to see whether these therapies were evading the virus.

"HIV was such a challenging virus that we had to come up with newer and newer technologies," said Neal Padte, Ho's longtime collaborator. "So when SARS-CoV-2 broke out, we had a toolbox ready."

The timing — if this can ever be said of a pandemic — was fortuitous. Before Covid-19, Mascola and others researchers were finally nearing, well, *something.* It's not quite a vaccine, though it may yet lead to one. Instead, it could turn into one of the best consolation prizes in the history of medicine, a byproduct of the vaccine hunt that may ultimately prove nearly as useful: a set of ultra-rare, Y-shaped molecules that, at least in animals, could neutralize most strains of HIV, potentially protecting at-risk people for months or a year and offering a path to new treatments.

The story of how researchers arrived at these so-called broadly neutralizing antibodies over the last 30 years is one of the hidden stories of everything that went right about America's pandemic response, the silent engine behind the vaccine and, particularly, the most effective treatments: antibody therapies from Vir, Regeneron, and Eli Lilly.

It may also be the story of how the US prevents infectious disease broadly in the future. For the first time, HIV vaccines based on Mascola's research are entering humans. And while prospects for success remain cloudy, he and his collaborators' work may yet prove key to responding to a broad suite of pathogens and achieving one of virology's new holy grails — a vaccine and a treatment to prevent a coronavirus outbreak from ever recurring.

"HIV is the most variable virus there is out there, so if you can deal with HIV, you can deal with anything," said Dennis Burton, a Scripps researcher commonly regarded as the father of the HIV antibody field. "It has pushed researchers to the limit."

The organized hunt for a broadly neutralizing HIV antibody began in earnest 20 years ago, after the International AIDS Vaccine Initiative, a non-profit founded in 1996 by the Rockefeller Foundation, hired a lanky and bushy-haired ex-professor named Wayne Koff as head of research. Like Moncef Slaoui in Operation Warp Speed, Koff was tasked with collating and expanding the pipeline of HIV vaccines. Except Koff had millions instead of billions to spend on a problem that — affecting primarily gay men, people in the developing world and IV drug users — rich nations and companies addressed with far less urgency.


Wayne Koff

By then, the world's hopes for an HIV vaccine had already been deflated repeatedly. When French researchers first isolated the virus in 1983, scientists at Merck and a University of San Francisco spinout called Chiron were nearing completion of the hepatitis B vaccine. It was a landmark moment in vaccinology. The first vaccine to use recombinant DNA technology, its success inspired the same enthusiasm that mRNA has today. HIV, it seemed, was just a matter of time.

"We actually thought it was going to be easy to make vaccines for all viral diseases," said Nancy Haigwood, who worked for Chiron at the time. "But then HIV turned out to have quite a few number of tricks up its sleeves."

Virtually all early constructs failed in the lab or in animals, a phenomenon with which Koff was well-acquainted. In 1990, as head of vaccine research at the NIH, he hailed how new discoveries "cracked open the door" to a shot. By 1993, working to build his own vaccine at a biotech, he acknowledged that most of the candidates that had captured the world's attention had failed basic lab tests.

Mascola at a briefing with Anthony Fauci and President Trump on March 3, as the nation's top physicians scrambled to address the new virus. Mascola at the time was already developing an antibody treatment for the new virus. (Photo by Brendan Smialowski / AFP) (Photo by BRENDAN SMIALOWSKI/AFP via Getty Images)

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Koff was ostensibly hired to get more candidates into human trials around the world, as the US would do effectively for Covid-19. But he soon believed that was the wrong task.

First, he decided, researchers would have to figure out what protection from HIV even looked like, literally. He invited 11 top scientists to a pair of meetings in Amsterdam and New York to hash out a plan.

“We realized very, very quickly that HIV vaccine development wasn’t a product development problem. It was a discovery problem,” said Koff, who now runs a non-profit dedicated to studying vaccine immunology. “If Covid-19 had the envelope protein that HIV does, we still wouldn’t have a vaccine today.”

A spherical shield around the virus, the envelope is one of HIV’s most powerful weapons. To understand just how devious it is, a contrast with Covid-19 is instructive.

Antibodies have been the heroes of Covid-19 immunity. Swarming through your bloodstream are 10 billion B cells, each carrying a slightly different antibody on its surface. These amazingly eclectic Y-

shaped molecules, produced by random shuffling of DNA, act first like an army of sentinels. When one latches onto a foreign protein, it starts making copies of itself and spitting out thousands of antibodies per second. Ideally, these antibodies latch onto a part of the virus and interfere with its ability to infect cells, a process called neutralization.

When SARS-CoV-2 enters the body, it makes little attempt to hide its spike protein — that now famous grappling hook — and, for all the concerns about variants, it can't readily change the spike's structure. Within 7 days, most patients are teeming with neutralizing antibodies that can glom onto the spike and prevent it from hijacking cells, one of the reasons most people clear the infection so quickly.

Give someone a vaccine encoding for the spike protein and within two weeks, they'll have swarms of neutralizing antibodies coursing through their blood, an army waiting to fire.

"The RBD — the notorious RBD — is just sitting there like a target that says 'hit me,'" said John Moore, an HIV researcher at Cornell University, referring to the receptor-binding domain that sits atop the spike. "And the equivalent on the HIV envelope just does not exist."

The HIV's envelope makes sure the virus doesn't fall prey to the same fate. First, it's studded with a forest of glycans, vibrating sugars that form a defensive canopy around the virus. The bigger problem, though, is that the envelope can mutate so rapidly that even if the immune system finds an antibody that neutralizes some strains, other strains within the same person will evolve their way around it. The antibody will become useless.

The first HIV vaccine ever designed, a construct Genentech first put into humans in 1987, elicited plenty of antibodies in volunteers. But not one of them effectively neutralized the virus.

"The virus always wins," said Burton.

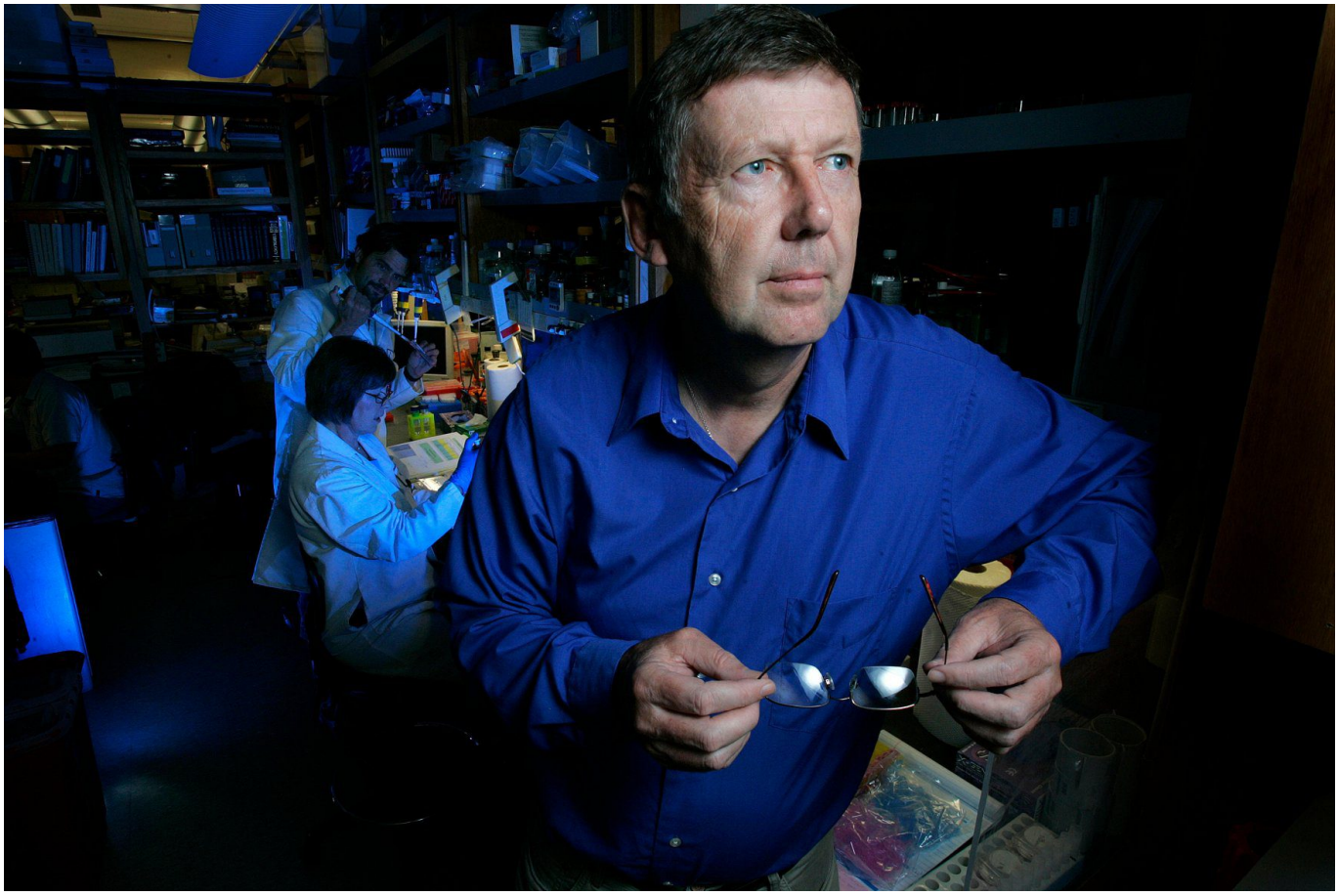
Well, almost always. Early on, researchers learned from studying the blood of patients that a tiny subset of HIV patients kept the virus in check. And that pointed toward a solution. If someone could figure out what was happening in those patients — if they could isolate one of those antibodies — then maybe they could reverse engineer it: figure out what it looked like, how it bound to and disrupted the virus and design vaccines that could induce healthy people to produce replicas.

"The first observation was that the natural immune response to HIV in some people – *some* people — was much better than anything we could get with the vaccine," Mascola said. "So then the question was pretty obvious: What's in these people's serum?"

Fishing individual — sometimes called monoclonal — antibodies out of serum, the yellow soup left over when you dump all the blood cells out of blood, wasn't easy then. The original method,

pioneered in 1976, involved taking a B cell from a mouse and fusing it with a cancer cell to create an immortal, antibody-pumping hybrid cell.

It was Nobel Prize-winning stuff, sparking hopes for drugs for all sorts of diseases. But, like many things in medicine, it worked best with mice. “And it turned out that it’s a lot more difficult to get human monoclonal antibodies,” Burton said.



Burton at his lab in San Diego at 2008, as he and and IAVI neared their first breakthrough

Burton, who at 69 has a full head of gray-white hair, a quick laugh, and still plays football (the British kind) once per week, made his name by developing a new approach while on sabbatical at Scripps in 1989. At the time, Richard Lerner’s lab there was racing with a Cambridge group to isolate the DNA of an antibody and grow it in bacteria.

When he arrived from a Swedish university, they were trying to grow just a portion of the antibody, but it wouldn’t form. Burton suggested to the graduate student leading the project that they grow the whole thing.

“And unbelievably, when I looked back on it, he listened to me straight off and said ‘right,’” Burton said. A few Fridays later, Burton went downstairs to find his photoplates glowing black, signifying the lab-grown antibodies were binding to their target. They cracked a bottle of champagne that Burton still keeps on his shelf today: “It just opened up the whole antibody field.”

Burton stayed at Scripps, enticed by the science and the San Diego sun. Immediately, he started using

his new technology on HIV, believing it held a path to a vaccine.

It was an unpopular opinion. At the time, most leaders — 90%, he estimates — in the nascent HIV vaccine field focused on T cells. Many doubted that a broadly neutralizing antibody could ever be found, and Burton had trouble just securing monkeys for his studies.

But in 1994, he isolated an antibody called B12 that neutralized two vastly different strains and protected monkeys from exposure to those specific viruses. It proved his idea was possible, but ultimately the antibody "wasn't all that broad and wasn't all that potent," Koff said. Most viruses escaped. The technology was still too primitive.

"I mean it was really, really difficult," said James Crowe, who runs a lab at Vanderbilt and invented the Covid-19 antibodies AstraZeneca is now developing. "It was a miracle if you could make one antibody in a year."

After the meetings in Amsterdam and New York, IAVI and the NIH established the Neutralizing Antibody Consortium in 2002 to try to accelerate the hunt. They brought together researchers from four different labs, a number that eventually grew to 18, combining immunologists, virologists and structural biologists. They tried to establish new standard procedures for isolating antibodies, testing their neutralizing ability, comparing them to other antibodies and turning the best ones into vaccines.

A rare example of science without ego, the consortium effectively centered around separate efforts at Scripps and the Vaccine Research Center. Mascola, a Bethesda native, was deputy chief of the center at the time. He arrived in 1999 after a post-med school stint at the Walter Reed Army Institute of Research analyzing the virus and why some of the first vaccines had failed, where he came to some of the same conclusions about the importance of antibodies as Burton.

"He's very collaborative," Burton said. "Not the type to be involved in a dirty race."

The big break started in 2006, when Koff and Burton launched "Protocol G." So few patients made antibodies that neutralized HIV that to find them, scientists would have to look around the world. Over the next 3 years, Koff teamed with local medical centers to collect antibody samples from 1,800 HIV patients across the globe, largely in Africa.

They selected for those who had been infected for at least three years, yet hadn't become sick. The body tends to make the best antibodies after prolonged exposure to the virus because the immune system evolves with the invader, selecting over time for the best defenders — a fact that would eventually throw a wrench in Burton and Mascola's vaccine efforts.

All those donors posed a problem: How do you screen them? Only patients whose sera could neutralize numerous disparate HIV strains would be useful, so you would need to match dozens of viruses with thousands of samples. “And that’s when we started using robotics,” Burton said.

They enlisted a diagnostics company called Monogram to throw hundreds of sera samples against tens of viruses at once. It worked. In an initial study, about 1% of the 1,234 donors screened were identified as “elite neutralizers.” Something in their blood had outwitted HIV.

Koff and Burton didn’t have a plan for how they could turn those elite neutralizer samples into antibodies, but the gold rush for antibodies in cancer — powerful new drugs like Herceptin and rituximab — had brought startups with new technologies into the fray. Burton called a biotech in Seattle called Spaltudaq, told them they should be working on HIV instead of cancer and offered them half a million dollars for each sample they screened.

Spaltudaq took 30,000 B cells isolated from one of the neutralizers and turned them into so-called supernatants, putting each into an individual well and stimulating them to pump out pools of antibodies. Testing each pool against a panel of viruses, they found two could neutralize most.

Back at Scripps, a prolific new graduate student named Laura Walker dropped everything and began studying how the two antibodies bound to the virus, hoping it could direct the path to a vaccine. The paper appeared in *Science* in 2009, pointing to the first two powerful antibodies against HIV.

”Laura just ran with it,” Koff said.

The breakthrough began to rekindle interest in HIV antibodies, a shift that accelerated that December with a finding out of Thailand. A vaccine trial there had once again failed. But unlike previous trials, a small subset, 30%, appeared to have been protected for a year and their serum seemed to contain antibodies.

“Everyone was caught by surprise,” said Mohammad Sajadi, an HIV researcher at University of Maryland. “And that really opened [things] up, put the focus back on antibody.”

Everything was clicking. In Bethesda, the Vaccine Research Center was also nearing a discovery using a slightly different approach. Rather than separating and analyzing all the B cells from a patient, researchers took those B cells and pooled them together. Then they took one part of the HIV envelope they knew was vulnerable — in many cases, a protein that the NIH’s structural biologists had identified— and used it as a fishing hook for the best antibodies.

In 2010, they found one that could neutralize 90% of the viruses thrown at it. Mascola presented the results to his colleagues in a conference room on the fourth floor, showing a color-coded table representing how well each of several antibodies could neutralize 190 strains of HIV. Green meant it

barely bound, red meant a potential drug.

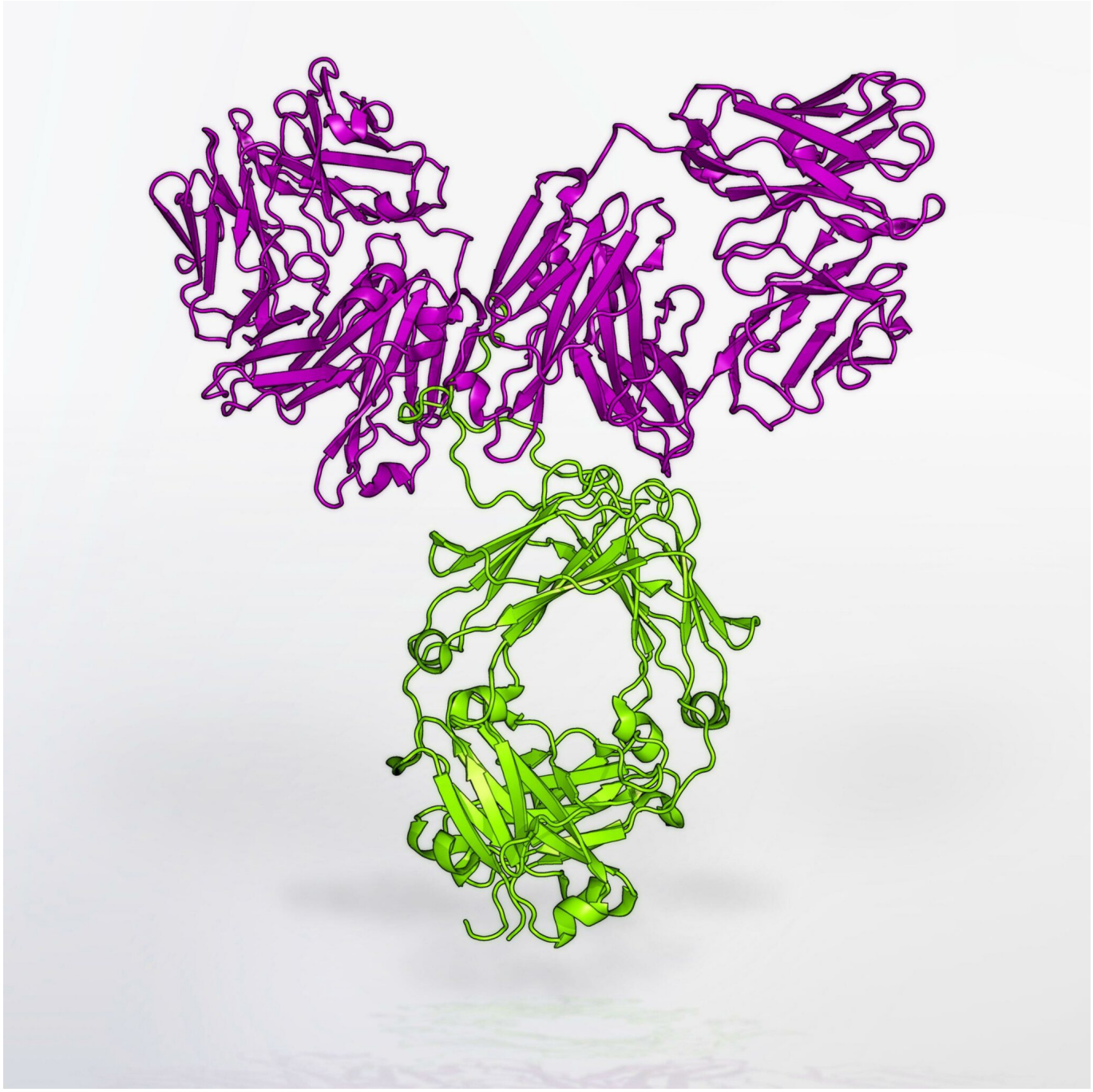
Nearly all of the rows for the antibody, called VRC01, were bright red.

“It was really unprecedented,” said Gary Nabel, the director of the Vaccine Research Center at the time. It forced him to think about his life’s work differently. “The first thought that popped in my mind was, wait a minute, do we have it backward?”

VRC01 re-energized and reshaped the course of HIV vaccines. Longtime skeptics of Burton’s approach dove into antibody work. Burton, Mascola and others identified hundreds more neutralizing antibodies and set about designing vaccines based on the parts of the viruses to which those antibodies.

“There was tremendous excitement,” said Shelly Karuna, an HIV researcher at Fred Hutch.

Nabel and Mascola, though, wondered if instead of reverse-engineering a vaccine, they could just manufacture large doses of the antibody and infuse them into patients. The antibodies wouldn’t last forever and they wouldn’t be cheap (antibodies cost orders of magnitude more per dose to produce than vaccines) but they might protect people for a while and offer a stopgap until a vaccine became available.



A model of the VRC01 antibody. The purple regions latch on to the part of the envelope HIV uses to enter immune cells.

The strategy had been tried before, most notably with an approved drug to protect at-risk kids from respiratory syncytial virus. In HIV, it had the potential to not only prevent but also treat — on the back of each antibody is a beacon that might signal the immune system to clear HIV-infected cells, something that could be essential for an eventual cure.

There were risks, though, to developing VRC01. Industry wasn't much interested because the science remained too speculative and most companies weren't interested in infectious disease, meaning the center would have to somehow make the antibody itself. And they knew some strains would still be impervious to VRC01 — should they wait for one better to come along?

But they decided — after meetings with Nobel winner David Baltimore, renowned vaccinologist Stanley

Plotkin, and other advisors — that they needed to at least test the concept.

“We knew that a vaccine that could induce these antibodies was a long way off,” Mascola said.

And as the months went by, they gained new reasons for putting the antibody into people. The antibody hunt was supposed to point them to a vaccine, but it quickly pointed to just how hard a vaccine would be. The first constructs Burton, Mascola and others built based off their prized antibodies failed to produce those same antibodies in animals.

Broadly neutralizing antibodies for HIV, it turned out, were strange molecules. Many of them bound to both the virus and that vibrating glycan forest, something few antibodies do. They had long loops rarely found in other antibodies. Their genetic code contained weird insertions and deletions.

In hindsight, the strangeness may not have been surprising. After all, these antibodies are distant outliers, a tiny fractal of the tens of thousands of B cells isolated from just 1% of HIV patients. They were the products of an immune system evolving over years living with the virus, selecting for the best antibodies over and over again as the virus tried to evade each innovation.

But it meant that HIV researchers would have to invent a new strategy. They would have to somehow figure out a way of coaxing a healthy immune system down that same path these rare patients had followed, something that no one really knew had to do.

“Logically, it should work,” Burton said. “What we didn’t anticipate at the time was how long that path would be.”

VRC01 would be the best way forward for a while.

VRC01 would soon offer its own disappointments. Mascola set up the Vaccine Researcher Center’s 2,000-liter bioreactor to churn out kilogram after kilogram of antibody — far more material than the center had ever produced — and NIH and US Army labs set up a series of trials in healthy volunteers and then HIV infected patients.

Trevor Crowell, hired as a new physician at the US Military HIV Research Program in 2014, remembered flying out to Thailand for intense five-day trips to set up a trial there on HIV patients. The study would take volunteers off their medication to test whether VRC01 could keep the virus suppressed on its own.

In theory, the trial was blinded and placebo-controlled, but back in Virginia, the results became clear rather quickly. Crowell got an email every time a volunteer had their virus rebound and had to go back

on meds. The updates came in swiftly.

“It was disappointing,” Crowell said, though he noted one patient on VRC01 did keep the virus suppressed for 40 weeks, which he called “a glimmer of hope.”

A pair of studies from the NIH and the AIDS Clinical Trial Group reached the same conclusion. By the time the novel coronavirus rolled around, only one major trial was left: a 4,500-person study to conclusively test whether the antibody could prevent remission.

VRC01 may have neutralized 90% of viruses, but practically, with the levels of antibody you could infuse in people, it protected against a far lower percentage of strains worldwide.

It “was an awakening,” said Katharine Bar, a University of Pennsylvania researcher who led two of the studies.

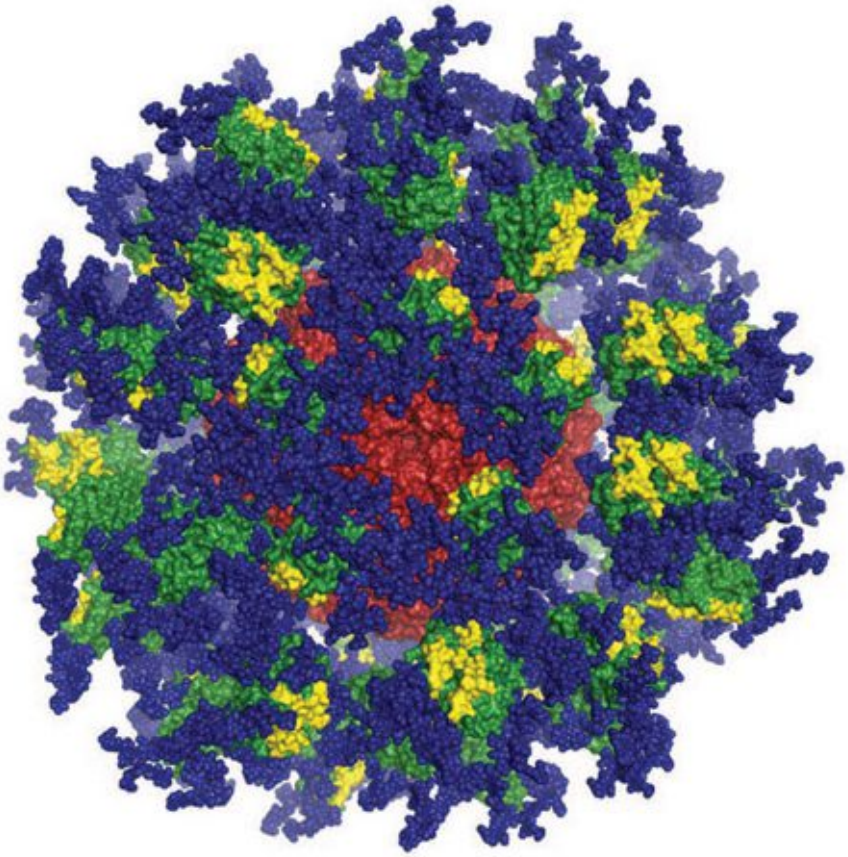
Yet even as a vaccine or treatment for HIV receded further into the distance, the Neutralizing Antibody Consortium’s work began popping up against other viruses.

In 2013, Jason McLellan, a structural biologist who worked with the Vaccine Research Center on identifying how Mascola’s antibodies bound to HIV, left the NIH to start his own lab at the University of Texas at Austin. He reached out to Peter Kwong, the chief structure biologist on the HIV project, and Barney Graham, Mascola’s deputy, to try another spin on the concepts the consortium was struggling to apply.

“To me, it was unclear clear whether these concepts … weren’t working because they were bad ideas, or because HIV was just a really hard virus to make a vaccine for,” McLellan said. “So my idea was: Why don’t we apply these principles to a more tractable virus?”

The most obvious case was RSV, the second-leading killer of small children in the world after malaria. Vaccines for RSV were an infamous failure; one candidate in the 1960s actually turned out to enhance the disease. But scientists had found an antibody, marketed as Synagis, that could protect the highest risk children from infection. Protection had to be possible somehow.

A vaccine made by reverse engineering VRC01, now in development with Moderna



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McLellan took Synagis and a couple other neutralizing antibodies and studied how they bound to the fusion protein, RSV's equivalent of a spike protein. When RSV reaches a cell, it changes the protein's shape for entry. McLellan discovered that the antibodies bound only to the pre-fusion form of the virus, not the post-fusion structure that everyone had been making.

With some tricky structural biology techniques also borrowed from HIV, they swapped some amino acids to create a stable version of the post-fusion protein. Overnight, it became one of the world's leading candidates for RSV.

McLellan then used the protein to engineer new antibodies for the virus, including nirsevimab, which AstraZeneca licensed and is now preparing to launch as the new standard-of-care for RSV.

"I don't think we have to be embarrassed about the progress because it's amazing," Crowe said, predicting McLellan's RSV vaccine candidate will be approved. "And all these other fields are benefiting."

Nabel and Anthony Fauci proposed applying the same approach to develop a universal vaccine for the flu, another highly variable virus. A vaccine roughly based on their blueprint recently showed promising effects in Phase I.

For Burton, the isolation of HIV neutralizing antibodies "lays down a marker" for what's possible: If you can find an antibody to HIV, you can find one to anything.

And in 2016, Mascola did. Teaming with a Swiss startup called Humabs that had developed a more advanced form of the NIH's B cell sorting technology, the agency identified a single neutralizing antibody against Ebola. After the virus returned to the Congo in 2018, it proved to be one of the first two effective treatments for the deadly virus, bringing survival rates to nearly 90% when given early in infection.

Meanwhile, McLellan started applying what he learned from RSV to a novel coronavirus outbreak in the Middle East called MERS. He figured out that, with a similar amino acid swap, he could make a stable version of the virus' spike protein for the first time. It would be crucial for a vaccine, which Graham wanted to design just in case another coronavirus broke out again.

When Mascola learned of a new virus circulating in Wuhan, China, he walked upstairs to a collaborator's office and started planning. This "could be the culmination of a life's work," he later told *Wired*.

Since 2009, other companies and researchers had expanded on the techniques they used to develop VRC01. One, a little-known but well-connected Vancouver biotech called AbCellera, developed a microfluidic chip that could sort millions of B cells within days. In 2018, DARPA, the defense agency behind weather satellites and the internet, gave the company a $30 million contract for a pilot project to test whether it could develop an antibody against a virus in 60 days.

In mid-January, after the first case struck the US, Mascola and Graham called CEO Carl Hansen and suggested they ditch the pilot and start on Covid-19. AbCellera had the advanced platform, but it would need Mascola's infectious disease expertise. "He immediately agreed," Mascola said of Hansen.

Calling hospitals and clinicians to obtain the proper ethical reviews, Mascola managed to get a blood sample from the first US patient, a man in Seattle, and shipped it off to Vancouver. Over three days, AbCellera screened 5 million cells, found 500 antibodies against the spike protein, whittled those to 175, and sent the sequences over to the NIH.

Everyone knew isolating a neutralizing antibody for Covid-19 would be easier than isolating one for HIV, but doing it so quickly posed its own problems. In HIV, researchers had sought out thousands of blood samples from the tiny sliver of patients who were best at attacking the virus. For the first Covid-19 antibody, Mascola had one sample, from a man chosen by fate to be first.

"We must have looked at over 100 antibodies," Mascola said. "And only one of them was good."

Future samples from other donors would prove more potent. But they didn't have those then, and with Eli Lilly agreeing to come on as a partner, they began develop what would later be known as bamlanivimab. Although it would eventually be pulled out of circulation because it wasn't effective against virus variants, early data showed it reduced the risk of hospitalization in patients exposed to the original virus. Nearly 800,000 doses were shipped across the country.

Moderna, Pfizer and J&J all used McLellan's modifications in their vaccines. Other antibodies, from Regeneron and Vir, which bought Humabs in 2017, also relied on similar technology to what was used to find VRC01. The NIH used the knowledge and infrastructure it gained from the then-ongoing VRC01 prevention study to get those quickly through clinical trials. Even the animal models used to verify the antibodies relied on HIV work, Shelly Karuna said.

It was an "unexpected benefit," she said. "All of these years of effort and HIV monoclonal antibodies have come to fruition."

A nurse in California receives an infusion of bamlanivimab, a Covid-19 antibody Mascola co-developed based off his HIV work (Irfan Khan / Los Angeles Times via Getty Images)

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The most direct benefit from the HIV field, though, could come in preventing future pandemics. Laura Walker, who went to the antibody specialist company Adimab after co-discovering the first HIV broadly neutralizing antibodies, last year co-founded a new company called Adagio.

With a $300 million IPO this month, the company has now raised nearly $800 million for an approach that looks markedly similar to what Walker and Burton did in HIV: collect serum from numerous donors and screen for a handful of antibodies that can not only neutralize one strain of coronavirus, but virtually all strains.

The goal is to develop a variant-proof antibody that could protect against all SARS-like viruses, giving the world a potent treatment against this virus and any similar virus that may one day spill over into humans. A first candidate is now in clinical trials.

Burton, meanwhile, has been collecting similar antibodies in his lab, but with a different goal. As with HIV, he wants to reverse engineer these universal coronavirus antibodies into a universal coronavirus vaccine. He, along with top officials at the NIH, have called for funding for a multi-billion dollar effort to do the same for all viruses that have pandemic potential.

Virus-family vaccines have never been made before. Inoculations tend to be made for a specific virus — a Covid-19 shot won't work well against SARS and it'll be even worse against MERS. But it could prove the best weapon to prevent the pandemic. And Burton's HIV approach — of finding the best antibodies and slowly coaxing the immune system to make them — could be the best path.

"It's all about getting a level of control you don't usually have. You're not looking for any old antibody, you're looking for a precise antibody and for that you need a precise vaccine," Burton said. "That's a level of sophistication we haven't reached, but we have the tools to do that now. And we need to do that, because the pathogens are obviously getting more sophisticated too."

Last January, as Covid-19 raged through the US, the results from the last VRC01 trial came back. It was a failure. Volunteers on placebo contracted HIV at the same rate as volunteers who received antibody.

"It was sobering," said Mascola. "A single antibody wasn't going to be enough."

Sequencing data from infected participants showed VRC01 protected against a subset of strains, but it was going to take broader and more potent antibodies to actually prevent infection. Researchers are now testing those, bringing a combination of antibodies into the clinic in hopes that hitting two spots on the virus will it make it harder for HIV to evade. Nabel, who left the NIH to be CSO of Sanofi from 2012 to 2018, even developed a trispecific antibody to hit three spots. He is now developing it as part of his new company ModeX.

Many of these antibodies have been engineered to stick around in the blood for six months or a year, potentially providing long-term protection and an attractive alternative to the daily pills that have long

dominated HIV prevention. They might also be safer.

But those pills are already known to be highly effective and companies, including Merck, Gilead and GlaxoSmithKline, are now making long-acting versions, raising questions about where exactly antibodies can fit.

“They’re going to have to compete in an environment right now where there’s very effective small molecule prevention approaches,” Bar said.

A vaccine seems an even longer way off, as early attempts to coax the immune system struggled. But Mascola noted that VRC01 has already changed the field.

The leading candidate, designed by Bill Schief, Burton’s colleague at Scripps, is designed to create what have become known as “VRC01-like antibodies.” There were promising results in a Phase I trial and now Moderna, with some fanfare, is making an mRNA version.

Still, neither Burton nor Mascola will tell you an HIV vaccine is a few years away; there have been enough of those predictions over the years. And yet, pleased as they are by the results in coronavirus and RSV, they’re not content either.

“The legacy, the early success is going to come with other viruses: Ebola, RSV, influenza coronavirus,” Mascola said. “But I think as scientists and public health officials, you look at HIV as a pandemic. Yeah, you say, ‘Well, it’s harder and we haven’t figured it out yet.’ But we’ve made some huge strides, and all the things we learned from coronavirus and RSV and influenza actually teach you in the reverse direction.”

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