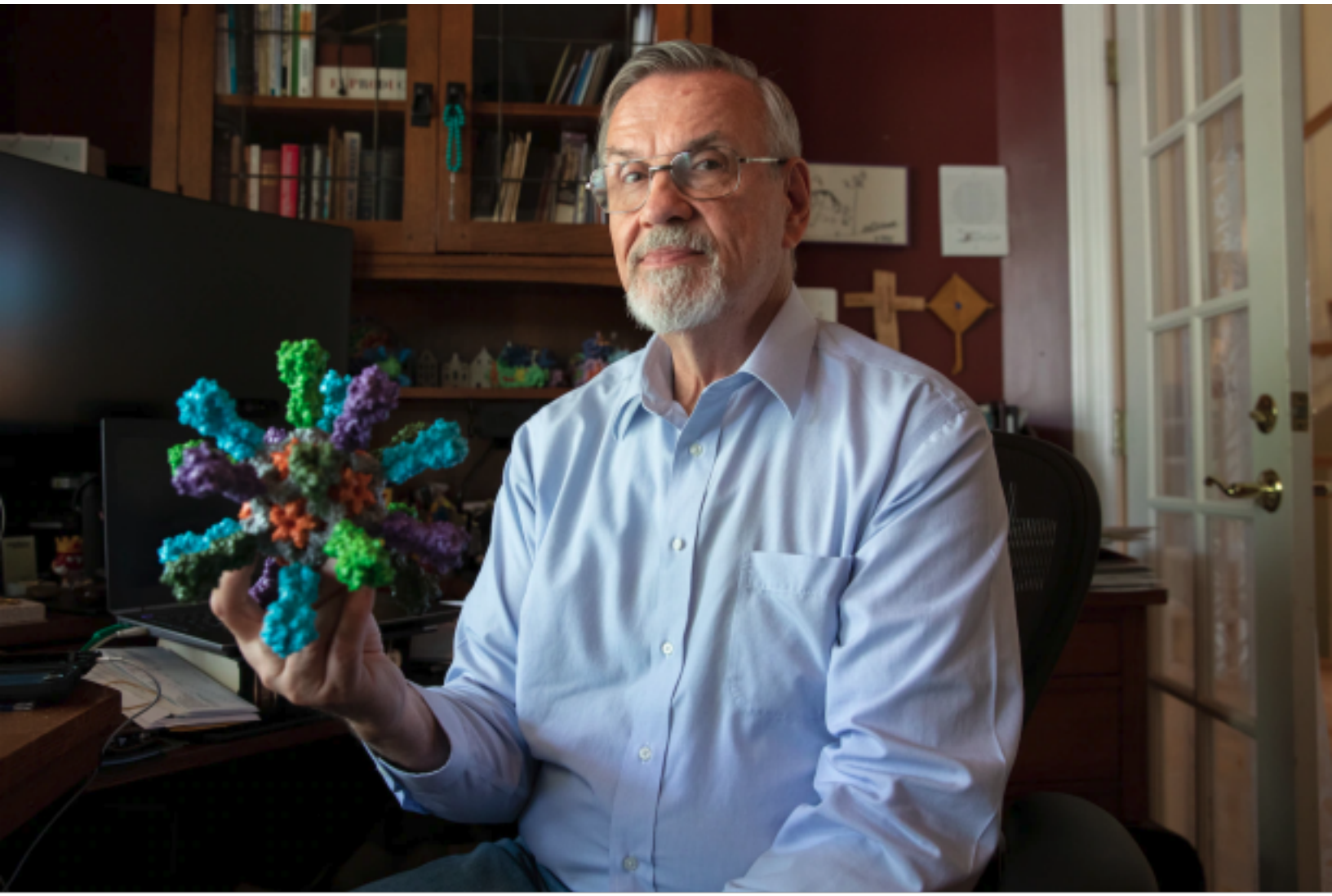
# Serendipity and foresight prepared the world to fight the coronavirus

Barney Graham laid the groundwork for the world to battle this pandemic, and the scientists he mentored will equip us for the next one



Barney Graham holds a model of a mosaic nanoparticle influenza vaccine in his home office in Rockville, Md., in July. When the coronavirus pandemic hit last year, the scientist's team at the National Institutes of Health raced to develop a vaccine. (Amanda Andrade-Rhoades for The Washington Post)

By Carolyn Y. Johnson

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Weeks before the pandemic was officially a pandemic, vaccine scientist Barney Graham spent long days in a public health war room in Geneva.

The death toll from the novel coronavirus had just passed 1,000. Graham and hundreds of other experts descended on a massive circular table at the World Health Organization's headquarters for an urgent global brainstorming session: How could science help?

Coronaviruses had been on scientists' radars — two new ones had spilled into humans over the last decades, causing epidemics of lethal pneumonia. But in the world of virology, coronaviruses were a bit of a backwater. Graham's laboratory at the National Institutes of Health in Bethesda, Md., was one of a small cadre that had maintained a steady focus on that family of viruses.

It was that lab that would help lay the scientific foundation for the vaccines that altered the course of the pandemic.

The trajectory of science is often shaped by accidents, foresight and luck. And Graham's role in shifting the path of the pandemic embodied that. The right team was in the right place to fight a health calamity sparked by an invisible enemy before anyone knew it was there.

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*This article is part of a series about the vaccine vanguard, the scientists who helped create coronavirus vaccines. Read about Katalin Kariko and Drew Weissman.*

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Graham and a tightknit group of academic collaborators had been studying the nooks and crannies of spike-covered coronaviruses for nearly a decade. Every month or two, they met with the world's coronavirus experts via conference call. He had forged a relationship with an up-and-coming biotechnology company, Moderna, that could design vaccines fast. His lifelong effort to increase diversity in science had culminated in a team of Black scientists who were ready to go. All the pieces were in place.

"We thought influenza would be the next one," said Barton Haynes, an immunologist at Duke University School of Medicine. "That was a brilliant insight Barney had: that he could see the future."

The future had arrived on that day in February 2020 in Geneva.

Kayvon Modjarrad, another scientist at the meeting, recalled the mood as uneasy. Global leaders were trying to hammer out a plan to speed up development of tools, including vaccines, to fight this new virus. But the knowledge gaps were huge.

After a long day of discussions, Modjarrad offered to take Graham out for dinner.

Years earlier, Modjarrad had worked in Graham's lab, researching coronaviruses as part of his portfolio.

Modjarrad knew Geneva well, because Graham had sent him there to work on the Ebola response in 2015. Graham, still a Kansas farm boy at heart, craved a burger.

At the best burger joint in Geneva, run by an expat from Brooklyn, they marveled at something that only those deeply embedded in the field could recognize: the sheer luck of it.

Out of two dozen possible virus families that could spark a pandemic, it was this — a coronavirus.

"Had it been any other kind of virus, they would have been ill-prepared," said Modjarrad, who now runs his own lab studying emerging pathogens at the Walter Reed Army Institute of Research in Silver Spring, Md.

Everyday life in the pandemic has been marked by the uneasy churn of devastating surges, new variants and a constant sense of foreboding about what the coronavirus might have in store next. But beyond the uncertainties of life in a public health crisis is a feat that appears destined to become one of the defining stories of the worst pandemic in a century.

Within a year of the first reports of an alarming new illness, scientists delivered remarkably effective vaccines. That doesn't mean the virus is vanquished. Scientists will be busy for years, making sure immunity doesn't fade and that vaccines stay ahead of the virus as it evolves.

But at the beginning of the pandemic, it was far from guaranteed that an effective vaccine could be developed. Then, in a plot line more typical of a Hollywood thriller than the disappointing, failure-filled trajectory of ordinary science, the first versions authorized in the United States were a spectacular success, exceeding all expectations.

Thousands of individuals contributed to the coronavirus vaccines, which were possible because of scientific teamwork on a massive scale. But the sprint to a vaccine depended on the meticulous labor of a visionary group of researchers. They are the vaccine vanguard, the people who invented the tools that will help wrestle the pandemic to the ground. Their insights and discoveries flew under the radar for years, until the world needed them the most.

# Farm to lab

Graham grew up in Olathe, Kan., his life subtly shaped by a different pandemic.

His granddaddy, a doctor, lost his first wife to the 1918 influenza pandemic. Graham's grandmother was his grandfather's second wife.

This twist of history didn't propel Graham directly into a career aimed at preventing deadly respiratory diseases, but Graham recognizes it now as an early example of the way history — personal and global — shaped his journey.

Graham spent his teenage years learning how to run a farm after his father, a dentist, bought one in Paola, Kan., and left it up to his two sons to figure out how to operate it. At its peak, there were 2,500 head of pigs to manage and 800 acres of crop to feed them.

He learned to solve problems and make mistakes. He and his brother burned down a barn. They got a tractor stuck in a lake bed. They were proudest of their corner fence posts, sinking them at least five feet in concrete.

Tucked alongside the scientific mementos and honors Graham has saved over the years is a framed "Graham Brothers Fence Construction" sign. "Done Right! Stays Tight!"

The farmer excelled at academics. When Graham started at Rice University, he thought he might become a math teacher. Biology turned out to be more intuitive.

It was in medical school at the University of Kansas that he began to think hard about the shape of life itself. He helped set up a microscope that scattered a beam of electrons to reveal structures so intricate they would be invisible with a regular light microscope.

To practice with the microscope, he would collect tiny things, coat them in a fine layer of gold dust and look, marveling at the fine details of a spider's eye.

In medical school, he met his future wife, Cynthia Turner-Graham. They were paired off as partners in a class on physical diagnosis, and they started talking: Graham about his misadventures on the farm, Turner about her music. She played the flute and went to school on a music scholarship, with the opportunity to perform with the legendary jazz composer Duke Ellington.

Turner-Graham loves to talk; Graham is reserved. People wondered what they had to say to one another.

"When we met and started dating, the fact that we enjoyed each other's company surprised us both," Turner-Graham said. "It started out as a curiosity."

Turner-Graham is Black; Graham is White. They quickly realized how much they had in common — little things, like their fathers were both dentists and they both drove Mustangs. And then there were the big things they shared, like the value they placed on family and faith. They discovered their lives echoed in ways that meant they could understand each other.

Within three months, they were engaged. Interracial marriage wasn't as common in the late 1970s, and some people on both sides of their families tried to discourage them initially. But, Graham said, "we basically just decided to listen to ourselves."

Around that time, Graham went on a rotation to the National Institutes of Health. Turner-Graham said she knew he would find his way back one day.

In the search for a place where they could do their residencies together, they settled on Tennessee. Graham served as chief resident at two hospitals, including Vanderbilt University Medical Center. Turner-Graham started at Meharry Medical College in a pediatrics residency, then left early to care for an underserved population at Bordeaux Hospital. She is a psychiatrist.

They juggled their medical careers with raising three children. Graham remained fascinated by basic science and, in particular, developed an interest in respiratory syncytial virus — better known as RSV — which can sometimes cause dangerous illness in the very young and the very old.

William Schaffner, an infectious-diseases specialist at Vanderbilt who mentored Graham, recently cracked open his "Barney Graham file" and found a paper towel he had tucked away decades ago. Scrawled across it in black Sharpie is a quick note, "I got it! — Barney" to let Schaffner know he had received a grant that would help support his nascent research career.

"I've kept it for these 30 years. Sometimes, it's good to be nostalgic and sentimental and a bit of a pack rat," Schaffner said. "It's just a token of affection and respect and warmth."

In the late 1990s, Anthony S. Fauci, director of the National Institute of Allergy and Infectious Diseases, was building a center at NIH to develop vaccines against HIV. The Vaccine Research Center would be a new model, designed to do basic lab science and bring vaccines through clinical development. Graham was recruited in 1999 to lead the clinical efforts in testing vaccines. He went, with the condition he could continue his lab work on RSV.

"We wanted fresh people who were coming in, fire-in-their-belly kind of people," Fauci said.

At 6 feet 5 inches tall, Graham is a towering figure with a stature in science to match. He is that rare person whose first name evokes immediate recognition.

In the world of academic science, often dominated by people with big brains, big egos and loud voices, Graham is soft-spoken and spare with his words. Graham, 68, tends to talk more about others' contributions than his own. He rose to become deputy director of the Vaccine Research Center, but seems most at ease when slowly rotating colorful, 3-D printed models of viruses in his hands, describing with grandfatherly warmth how the spiky protein on the coronavirus surface rearranges its loops and bumps to invade a human cell.

"Some people shout. Many people speak. Barney murmurs," Schaffner said. "You have to listen to him very carefully to follow and understand the profundity of what he is saying."

## 'Get ready for 2020'

When rumors swirled late in 2019 that a mysterious pneumonia in Wuhan, China, might be caused by a coronavirus, no one — not even Graham — could have known what would unfold.

"FYI. Get ready for 2020," he wrote before dawn on New Year's Eve to Kizzmekia Corbett, leader of the coronavirus team at his NIH lab, forwarding a news report about the outbreak.

A few days later, he called Jason McLellan, a structural biologist and close collaborator now at the University of Texas at Austin, interrupting McLellan's family vacation snowboarding in Utah to talk about the game plan.

Even if the threat from this virus remained contained — like Ebola and Zika, other viruses for which scientists at the Vaccine Research Center had launched projects — Graham saw an invaluable opportunity to run a drill he had been turning over in his mind for years.

Graham wanted to get ahead of emerging infectious diseases by building a library of prototype vaccines against each of the major virus families known to be capable of spawning a human outbreak. The research could be pulled off the shelf if a virus emerged and tweaked to fight the new threat. No matter what technology platform a vaccine used, whether new messenger RNA vaccines or more traditional protein vaccines, the information could be used to optimize the way it triggered the immune system. The world would have a huge head start.

Graham, in collaboration with McLellan, had already done much of that advance work on coronaviruses, through a mixture of foresight and serendipity. The path to the coronavirus vaccines began in Graham's long quest to develop a vaccine against RSV, the childhood virus discovered in 1955.

In the 1960s, scientists had attempted to make a vaccine against RSV, with disastrous results. Instead of protecting infants, the shots made the illness more severe. Vaccinated children were more likely to end up in the hospital when they got sick than those who were unprotected. Two children died.

"These findings were entirely unexpected," the scientists wrote. "We lack a definite explanation."

Graham had spent years trying to unravel what went wrong and build a vaccine that worked. In 2008, he teamed up with McLellan, who had been working on HIV, to tackle the problem with new tools and a fresh perspective.

Vaccines work by presenting the immune system with something that looks like the real virus — a "wanted" poster that teaches the body to recognize and block the intruder. RSV, they would discover, was a quick-change artist.

A key protein that decorates the surface of RSV morphs into a different shape after it breaks into cells. The vaccine that backfired had set the immune system on a hunt for the wrong misshapen villain. McLellan and Graham used a 3-D mapping technique to figure out the structure of the protein, identify new vulnerabilities and design a vaccine, one of Science magazine's breakthroughs of 2013.

They looked for the next target. Middle East respiratory syndrome, a coronavirus with a frightening fatality rate, killing 35 percent of its victims, had just emerged in Saudi Arabia.

Graham and McLellan saw what looked like a 10-year clock. Severe acute respiratory syndrome, caused by another coronavirus, had emerged in 2002-2003. Now, MERS. It seemed like a good bet the world might need a coronavirus vaccine in 2022.

"It was a great thing for a young researcher like me, starting my lab, to work on," McLellan said. "Let's try and figure out how to make, not necessarily a MERS vaccine, but something that would work for all coronaviruses."

Using the same playbook they had deployed against RSV, their labs and another at Scripps Research Institute showed coronavirus spikes had the same slippery, shape-shifting tendencies as RSV. They searched for ways to stabilize the spike used in a vaccine and found two tiny tweaks to its genetic code that could lock it into the correct mushroom shape. Those tiny changes could be deployed in a vaccine to make sure the immune system went hunting for the right intruder.

In 2017, it was a solution to a problem few people cared about.

That didn't faze the scientists chipping away at the work. Corbett, a talented and ambitious viral immunologist who had boldly announced to Graham when she was a college student that she planned to have his job one day, had recruited a small group of junior scientists to work on the problem with her.

Olubukola Abiona had always been interested in science but got hooked her senior year of high school when she worked in a university laboratory and had an epiphany: "Every line I learned in a textbook had an experiment behind it."

Corbett asked Abiona on the first day of her NIH job, fresh from her undergraduate degree, if she knew what a virus was. Abiona nodded, thinking she did, then listened as Corbett talked in detail about viruses — and then interrupted her.

"No, I don't!" Abiona burst out. She was a quick study and a hard worker, with a conscientious streak so strong that she thought something was wrong as she gained independence in the lab.

"You didn't check on me like you did before," she once told Corbett, worried.

"That's because I trust you," Corbett replied.

At the bench next to her was Geoff Hutchinson, who arrived at NIH after serving in the Peace Corps in Mozambique following college. After a lifetime of good health, Hutchinson fell seriously ill with a succession of undiagnosed infections and illnesses, losing a quarter of his body weight. He resolved to dedicate his life to developing vaccines and worked on the flu at NIH before joining Corbett's team.

"Flu was sort of like the favorite child, and everything else, less so," Hutchinson said. "But the flip side of that is that's also exactly what Kizzmekia wanted, because there's no reason the next pandemic can't be [a] coronavirus."

Cynthia Ziwawo, in search of a job to keep her mind sharp between college and medical school, had heard of MERS and SARS when she joined the lab a few months before the pandemic started, but she would soon develop deep expertise in running the tests for antibodies that bind to and block a coronavirus.

"It was a leap of faith," Ziwawo said.

Before every scientist in the world jumped into the field last year, Corbett and these three — Abiona, Hutchinson and Ziwawo — were there, ready to run an all-out first leg of the vaccine relay.

Early on Jan. 7, Stéphane Bancel, the chief executive of Moderna, a biotechnology company that had been working with NIH and had planned to develop a prototype vaccine against Nipah, a bat virus, sent Graham a brief email questioning what this new virus was.

Within minutes, Graham replied they didn't know yet, but they were ready if it turned out to be a coronavirus.

"We were waiting to have verified sequences before I called, but this would be a great time to run the drill for how quickly can you have a scalable vaccine," he wrote.

## Blueprint of the virus

Late in the evening of Jan. 10, the genetic blueprint of the coronavirus was posted online by Chinese scientists.

The race was on.

The next morning, a Saturday, Corbett texted Hutchinson and told him the genome was online.

He went into the lab and did the same thing scientists across the world were doing — taking the work that Graham and McLellan had produced years earlier on how to stabilize coronavirus spikes and applying it to the new virus.

The solution was sitting on the shelf.

The next challenge would be to generate lots of spike protein. The spikes don't just decorate the outside of the coronavirus, they enable the virus to latch onto cells and wreak havoc. Understanding the spike and finding ways to block it would be key to the vaccine effort. Graham often calls protein "the basis for everything related to vaccine development."

To make the protein, they would need tiny circles of custom-designed DNA called plasmids. In Austin, Nianshuang Wang, a scientist in McLellan's lab, realized the whole world would be ordering plasmids — and that the surge in demand could mean weeks of waiting.

As a backup, Wang ordered small, individual pieces of the plasmids that could be created faster. For more than a week, he and a colleague, Daniel Wrapp, strung them together, like beads on a necklace, sometimes working until 4 a.m.

McLellan's lab shipped the complete plasmids by FedEx to Bethesda. When the envelope arrived, Corbett sprinted into Graham's office. It was time to work.

Generating protein is a standard part of working in a molecular biology laboratory, but each step takes time and can be finicky — like following a complicated, days-long recipe that requires absolute concentration and can sometimes, inexplicably, fail.

Raw ingredients were beginning to be in short supply. Hutchinson and Abiona realized they needed more of an orange nutrient broth to grow cells for their experiments. They went around the Vaccine Research Center, asking for donations. Eventually, Graham and his boss told people to give Hutchinson and Abiona what they needed.

All of them were used to working long hours, but the pressure was new. Sometimes, Graham and Corbett would ask if they had the results from an experiment they were just beginning. They would work late to finish experiments — and then start analyzing the data that night.

"I need to actually have something to show," Ziwawo said. "This is bigger than just us."

Small differences in techniques can throw an experiment off, and Abiona and Hutchinson decided to work in parallel and with duplicate batches, constantly reviewing and checking to see if they could learn from each other.

"You can't waste a day. Where he did it one way, I did it another way," Abiona recalled.

Hutchinson's dreams, when he was able to get sleep, were about the lab. Abiona felt constant anxiety that an incubator would fail or a dish might get contaminated.

At the end of January, Graham was in Barcelona at a childhood pneumonia forum. At home, his team harvested the spike protein for the first time. This was a crucial first step.

The early experiments, Hutchinson recalled, suggested the protein might be "fragile and temperamental." They had lost some of the yield from the first batch. The first clue they had the right protein would be when they purified it, sorting it by size. It was one of the first moments they could exhale.

"It just perfectly lined up, like one nice, clean peak," Hutchinson recalled.

There was no time for celebration. A television crew was in the lab interviewing Fauci one day. The young scientists heard him say the vaccine would be in human testing within 100 days of the genome being posted. Hutchinson's and Abiona's heads jerked up, and they exchanged a surprised glance.

The magnitude of what rested on their shoulders began to come into focus. Sometimes, they would look around in wonder: The whole world was depending on these three, who didn't even have the post-graduate academic degrees that are the typical entry pass to the highest levels of science.

The weight of that pressure came to a head in March, when Ziwawo felt a tickle in her throat.

Coronavirus testing was still in short supply, restricted to people with a travel history. Ziwawo had a bad feeling but soldiered through a growing set of symptoms, hoping it was the flu.

"It's a pandemic. I need to get work done, but I feel terrible," Ziwawo recalled recently. "I'm shaking at my desk, but I have to run these assays. I don't want to halt things. And in retrospect, it shows just how much of a one-track mind we were, that getting sick my biggest worry is: Who is going to do these assays?"

Hutchinson was on his way into the lab to finish an experiment when he got the call that Ziwawo had tested positive for the coronavirus. He had to turn around and go home to quarantine. Abiona was living at home with her parents, both nurses. Her brother worked as a pharmacy technician. The fear that she would infect them, or vice versa, was huge.

"I'm working on the vaccine. I can't afford to get sick," Abiona said. "I don't have a replacement."

## A time to every purpose

Sixty-six days.

It took 66 days from the genome being published to the Moderna vaccine being injected into people.

They handily beat the timeline Fauci laid out, which had seemed so unachievable in the moment.

Last November came the news they had hoped and expected to hear: The leading U.S.-developed vaccines performed spectacularly well.

By that time, the vaccine effort had become an all-of-science effort. The Pfizer-BioNTech coronavirus vaccine received federal emergency authorization in December. Days later, Moderna's coronavirus vaccine, also based on messenger RNA technology, did too.

The core coronavirus team had begun to disperse, as the researchers moved on to the next stage of their careers. Ziwawo left first, for medical school. Then, Hutchinson moved to Seattle to work toward a graduate degree at the University of Washington. Abiona just started medical school, and is simultaneously pursuing a PhD. Corbett, who guided them all, established an independent laboratory at the Harvard T.H. Chan School of Public Health this summer.

Graham continued to put in long hours from his home office in Rockville, watching hummingbirds dart and hover at a feeder as he worked. Variants. Boosters. The list of things to do was endless. Behind it all was Graham's plan to prepare the world for future pandemics from any of the known viral threats. He estimates it's about 20 years of work for 1,000 scientists.

But Graham also began to feel impatient with the limits of science. Science had done its best, but there were gaps that couldn't be bridged at the lab bench.

Merely inventing the vaccines was not enough, Graham realized. Equity of all kinds is on Graham's mind a lot. In his 42-year marriage with Turner-Graham, they've had an ongoing conversation about privilege, bias and racism. Many of the themes have emerged in the pandemic.

Vaccination rates among the communities of color hit hardest by the pandemic lagged. Graham, his wife and Corbett went to a vaccine drive at their church, Corbett wearing a shirt that said, "A black girl will save the world."

There was a clear need to build manufacturing capacity in low- and middle-income countries, which would be the last to benefit from the vaccines.

Graham had planned to step down from NIH in 2020. He and Turner-Graham had hammered out a five-year plan long before the pandemic to relocate closer to their grandchildren in Atlanta. He thought by then he might have created a single product that could help people — a vaccine for RSV.

Instead, his work has led to multiple coronavirus vaccines, monoclonal antibodies against covid-19 and Ebola, and an RSV vaccine probably on the way.

Graham is vague on exactly what he wants to do next, but he has been studying the gaps. If most of the world doesn't have access to the vaccines, the pandemic will continue to burn. If the public doesn't understand biology, misinformation will flourish.

One afternoon, a few weeks before his retirement from NIH, he said a laconic goodbye to a collaborator and talked about the challenge ahead: reinventing himself.

"I'll have fun playing with the grandchildren," Graham said. "We'll see what I can do out there by myself."

*Alice Crites contributed to this report.*

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