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▲ Moderna's headquarters in Cambridge, Mass. PHOTOGRAPHER: TONY LUONG/THE NEW YORK TIMES/REDUX

## Moderna Wants to Transform the Body Into a Vaccine-Making Machine

The U.S. company and its German rival BioNTech plan to use RNA as a messenger inside cells to produce an immune reaction. The advance could

upend vaccine development long after the pandemic.

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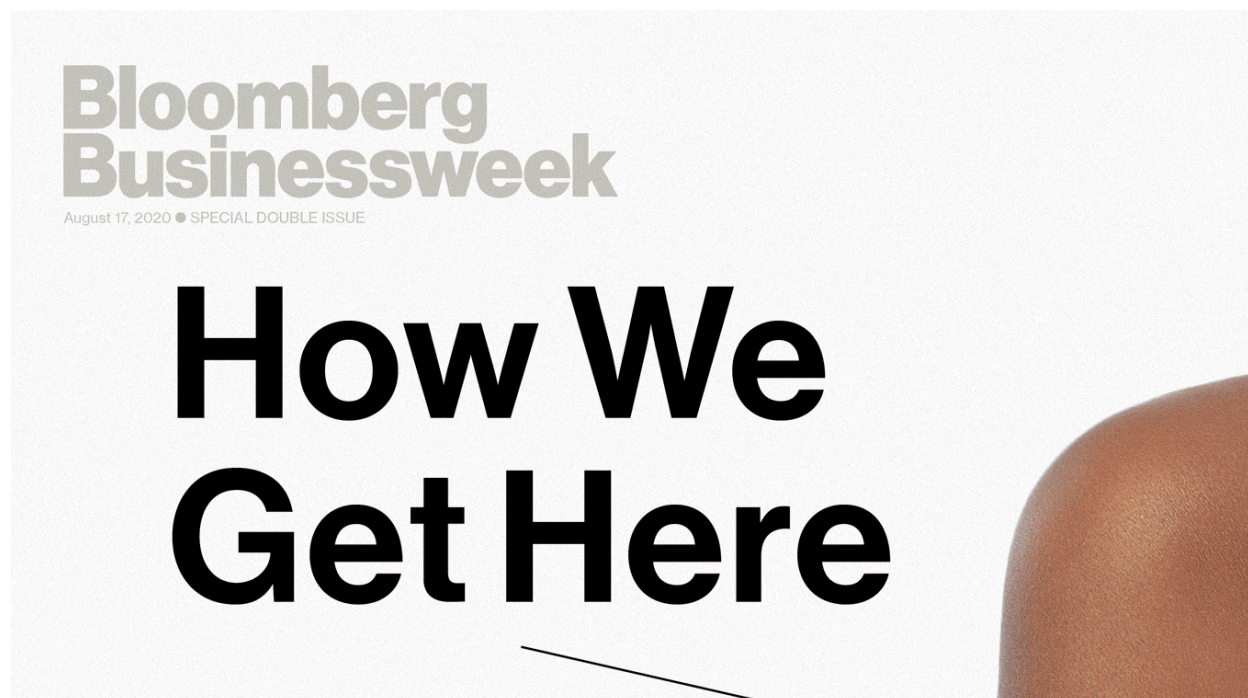
By Robert Langreth and Naomi Kresge



Almost every antiviral vaccine ever sold works in a similar way: A dead or weakened virus, or a piece of one, is introduced into a healthy person. The weakened virus stimulates the immune system to generate antibodies, protecting the person when the real pathogen threatens to infect them.

Over the decades, this tried-and-true approach has vanquished polio, eradicated smallpox, and reined in chicken pox, measles, and mumps. But vaccine production has never been simple or fast. Many flu vaccines are still grown in chicken eggs. Newer approaches draw on genetic engineering to eliminate the need for whole viruses, but their viral proteins are still grown inside live cells.

The coronavirus vaccines from Moderna Inc., in Cambridge, Mass., and its German rival BioNTech SE propose to immunize people in a radically different way: by harnessing human cells to become miniature vaccine factories in their own right. Instead of virus proteins, the vaccines contain genetic instructions that prompt the body to produce them. Those instructions are carried via messenger RNA, or mRNA.







The science,  
manufacturing, politics,  
and persuasion  
that just might end  
the pandemic  
**The Vaccine Issue**

▲ Featured in *Bloomberg Businessweek*, Aug. 17, 2020. [Subscribe now.](#) PHOTO ILLUSTRATION BY 731; GETTY IMAGES (9); ALAMY (4)

Moderna's mRNA-1273 consists of a strand of mRNA that tells the body to produce the spike protein the coronavirus uses to latch onto human cells. The strand is like one side of a zipper; the “teeth” are a sequence of chemical letters that cells read to produce the 1,273 amino acids that make up the spike protein. If the vaccine works as intended, the body will start producing the proteins soon after injection, prompting the immune system to react and build up protective antibodies against them.

The great advantages of mRNA vaccines are speed and flexibility. No finicky live cells or hard-to-handle viruses are needed, and the basic chemistry is straightforward. Moderna's vaccine reached Phase I human trials on March 16, only 63 days after the company began developing it. And at 6:43 a.m. on July 27, the first volunteer in Moderna's 30,000-person, final-stage efficacy trial in the U.S. received an injection. Less than 12 hours later, BioNTech and its partner, Pfizer Inc., said they, too, were beginning a late-stage trial, a study that will be conducted in the U.S., Brazil, and several other countries. They took advantage of mRNA's rapid-response capability to create four slightly different vaccines, which they compared in initial

trials before selecting the best one for large-scale testing.

In Phase I trials, both the Moderna and BioNTech-Pfizer vaccines stimulated people's immune systems to produce antibodies that neutralized the virus in lab experiments, a positive initial sign. "This is a relatively new platform, but it is looking quite good," Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases, said after the results of Moderna's Phase I trial, sponsored by NIAID, were published. "Neutralizing antibodies are the gold standard of protection." Moderna, which has worked with NIAID for years, is receiving \$955 million from the U.S. government to support its coronavirus trials.

How well mRNA vaccines will actually prevent Covid-19 remains unknown. No vaccine based on messenger RNA has ever been approved for any disease, or even entered final-stage trials until now, so there's little published human data to compare how mRNA stacks up against older technologies. And the vaccines have hardly been free of side effects: In Moderna's Phase I trial, all 15 of the patients who received the median of three dose sizes reported at least one side effect, though none were severe. Three of the 15 patients at the highest dose had temporary severe reactions. That dosage won't be tested further.

Still, the accumulating data has some mRNA skeptics warming to the technology. "I don't see the reason for focusing on mRNA vaccines. I don't get that," Peter Jay Hotez, dean of the National School of Tropical Medicine at Baylor College of Medicine in Houston, said in an interview in early June. "The old-fashioned vaccines may do a better job." In late July he said his opinion had shifted based on encouraging monkey and human trial results. Moderna's vaccine "is showing promise," he said. "There is enough of a glimmer to warrant continuing its clinical development and progressing to larger clinical trials."

The possibility of a Covid-19 shot has led investors to more than triple the value of Moderna's shares this year, giving the company a market capitalization of about \$28 billion, an astonishing number for a company with no products. BioNTech shares have more than doubled. A third company with an mRNA-based Covid-19 shot, CureVac AG, has said it's



considering an initial public offering. Both Stéphane Bancel, Moderna's chief executive officer, and Ugur Sahin, his less flashy counterpart at BioNTech, have become multibillionaires.



▲ Bancel at a March meeting of the White House Coronavirus Task Force. PHOTOGRAPHER: ANDREW HARNIK/AP PHOTO

The excitement around mRNA goes beyond the pandemic. Proponents hope it can become a wide-ranging platform that will lead to vaccines for other difficult-to-treat infections, as well as customized cancer shots and even heart disease treatments. “It’s a big moment for mRNA therapeutics in general, because now it’s a household word and everybody knows about it,” says Derrick Rossi, a stem cell biologist who was a co-founder of Moderna in 2010 but is no longer affiliated with the company. “For Moderna, it’s the first time on the global stage.”

Interest in using genetic material to turn the body’s cells into vaccine factories dates to a series of experiments in the early 1990s. In 1993 researchers at Merck & Co. injected lab mice with loops of DNA that contained instructions for influenza proteins. To the surprise of the scientists, the mice generated an immune response that protected against the flu. The concept, so elegant it seemed almost too simple to be true,

produced a surge of excitement among vaccine experts.

But though DNA vaccines worked in animals, they weren't successful in initial human trials. It was difficult to get sufficient amounts of DNA into human cells, and when scientists overcame that, the vaccines turned out to be less potent than needed. (They were tried on the most challenging diseases, including HIV.) Over the years research into DNA vaccines has continued, but none has made it to market for humans. Inovio Pharmaceuticals Inc., a dark horse in the Covid-19 vaccine race, is testing a DNA-based approach. It uses a hand-held device to zap the skin with electric pulses after an injection, opening up holes in cell membranes to allow in more DNA.

For years most researchers gave little thought to using messenger RNA as a vaccine or therapeutic, despite its close relation with DNA. When the body needs more of a protein, mRNA transports the requisite genetic code from the DNA to protein-making factories throughout the cell. But unlike DNA, a stable molecule, mRNA is notoriously fragile. Numerous enzymes present throughout the body break it down. Making matters worse for vaccine researchers, the immune system is hypervigilant about foreign RNA, identifying and destroying it before it can spur the protein-manufacturing process. In the 1990s, "we couldn't envision it being feasible," says Barney Graham, deputy director of the Vaccine Research Center at NIAID.

**“It was very clear to me this technology could be deployed one day in a potential outbreak”**

A few lonely scientists pursued mRNA therapies for years. In 2005, University of Pennsylvania researchers Katalin Kariko and Drew Weissman found that a slight modification to the mRNA molecule could reduce the immune reaction, making it much more amenable for use in drugs or vaccines. (Since then, scientists have found ways to reduce mRNA's other vulnerability inside the body, protecting it from enzymes by encapsulating it in lipid nanoparticles.) They filed for a patent and formed a company, but the university, which had rights to the patent, licensed it to a third party.



Moderna rose to prominence using a similar approach. The experience still rankles Kariko, who left Penn for a job at BioNTech in 2013. “My science and my work were not considered important, and I was not recognized,” she says. “Nobody cared.”

The idea started gaining more attention in 2010, when Rossi, then at Harvard Medical School, used modified mRNA to convert skin cells into stem cells. Sensing big commercial possibilities, he reached out to his Harvard colleague Timothy Springer, who’d made \$100 million in 1999 by selling the first biotech company he founded. Springer introduced Rossi to the venture capital company Flagship Pioneering, which founded Moderna in 2010 and began its operations the next year. He also brought in Robert Langer, a chemical engineer at MIT who’d co-founded many other companies. Langer became a co-founder and board member. (Springer, who put \$5 million of his own into Moderna, made \$400 million when the company went public in late 2018. His stake is now worth about \$1 billion; Langer’s is worth about \$900 million.)

Bancel, the former CEO of French lab testing company BioMérieux SA, joined the board in March 2011 and became Moderna’s CEO that October. He proved to be a prodigious fundraiser and a tireless proselytizer for the technology. In its eight years as a private company, Moderna raised \$2.5 billion in venture capital and drug-company money, leading to one of the biggest IPOs in biotech history.

Armed with so much funding, Moderna cast widely for possible targets for its technology, including rare diseases and cancer. In its early years it was an intense place with lots of turnover. Bancel “is very ambitious,” Rossi says. “He drove it very, very hard and drove people that worked there very, very hard.”

Moderna also gained a reputation for secrecy. For years it published few scientific papers, unusual for biotech companies, which typically like to brag about their credentials. Since 2017, though, it’s published more frequently; the company says it now has more than 50 publications.





▲ Tureci SOURCE: BIONTECH

BioNTech, the company that's emerged as Moderna's biggest competitor, was founded quietly in 2008, based on the research of a husband-wife team of German medical researchers, Ugur Sahin and Ozlem Tureci. Tureci had spent her girlhood following her father, a surgeon, on his rounds at a Catholic hospital staffed by nuns. Sahin's parents worked for a Ford factory in Cologne. The pair met while they were finishing their medical training; in the 1990s they were hired by Christoph Huber, head of the hematology-oncology department at the University Medical Center of the Johannes Gutenberg University Mainz.

The three of them spent years pursuing immune-based treatments for cancer, eventually zeroing in on personalized vaccines that attempted to enlist the immune system to attack tumors. The researchers screened databases of gene sequences to find markers on cancer cells that could alert the immune system to targets. In 2000, Sahin started exploring mRNA as a delivery method for cancer vaccines. All of this was considered a crazy idea at the time, Tureci says.

So when Sahin, Tureci, and Huber started Ganymed Pharmaceuticals in 2001, they focused on more proven immunological approaches. Then,



seven years later, Sahin persuaded two of Ganymed's investors, Thomas and Andreas Strüngmann, to spin out the mRNA cancer vaccine research into a new company—BioNTech. Sahin became CEO, and Tureci was on the scientific advisory board. In 2018, two years after Astellas Pharma Inc. bought Ganymed, she became BioNTech's chief medical officer.



▲ Sahin SOURCE: BIONTECH

If Moderna is polished and corporate, BioNTech has always had an academic vibe. The company has published its research from the beginning, putting out some 150 scientific papers in the past eight years alone. Sahin still uses his university email address. “Uğur is a scientist, and even though he runs a multibillion-dollar business, he still is a scientist and he thinks like a scientist first,” says Penn’s Weissman, who receives research funding from the company.

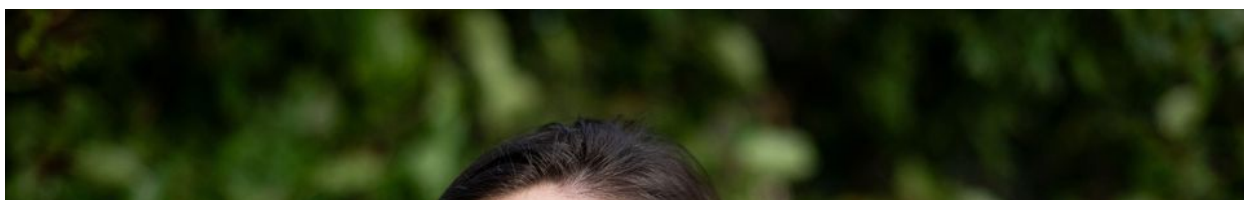
For most of its history, BioNTech focused exclusively on cancer drugs. Its first big foray into infectious disease came in August 2018, when it signed a deal with Pfizer to work on a vaccine for seasonal flu. The idea was to use

BioNTech's customization process to develop a better vaccine for the influenza pathogen, which morphs and mutates each winter season. Huber, a board member, says he never would have guessed its first product could be a pandemic vaccine.

Moderna was also initially focused on drugs. In 2014, Bancel recalls, a small group charged with finding uses for mRNA "were exploring new things, and they said, 'Hey, vaccines might be a great use of this technology.'" The potential was obvious. For any given vaccine, "we use the same process, in the same building, in the same rooms, with the same people. That gives you an incredible speed advantage," Bancel says. "It was very clear to me this technology could be deployed one day in a potential outbreak."

In 2017, Moderna started working with Graham's team at NIAID to design vaccines for several viruses, including MERS, a coronavirus that had hit Saudi Arabia and other countries starting in 2012. In the fall of 2019, Bancel briefed NIAID officials on a factory the company had built in Norwood, Mass., which could produce new vaccines in 60 days. They were skeptical at first, he says, because the company had never produced anything at scale, so he invited them to tour the facility and offered to do a test run for a hypothetical pandemic. The agency would send Moderna the genetic sequence for an emerging viral disease, and Moderna would see how fast it could have vials of a vaccine ready for clinical trials. NIAID was about to pick a virus to use when Covid-19 hit.

In early January, Bancel read a newspaper article about a mysterious virus going around China. He fired off an email to Graham asking if he knew what it was. Graham said he didn't, but if it was a SARS-like coronavirus, it might be a good time to run the pandemic vaccine drill they'd been discussing. Bancel forwarded the emails to Hamilton Bennett, who is now program leader for Moderna's Covid-19 vaccine effort. Bennett, a self-described "public-health nerd" with a master's degree in environmental microbiology, had sought a job at the company after hearing it was working on mRNA-based vaccines for new viruses. "It's one of the few technologies that could respond in real time and make a difference," she says.







▲ Bennett PHOTOGRAPHER: KAYANA SZYMCZAK FOR BLOOMBERG BUSINESSWEEK

On the evening of Friday, Jan. 10, the gene sequence from the virus was posted online by Chinese researchers. Scientists at NIAID and Moderna worked all weekend to identify a viable mRNA sequence for the spike protein. By early the next week they had agreed on one and started trying to synthesize a vaccine.

Bennett coordinated almost daily calls with NIAID and, in later months, numerous other federal agencies as they became involved. Moderna scientists were highly motivated to show that mRNA technology could help, she says. “Everyone looked at this as, I’m going to do whatever I can to make this successful.” The company originally thought it could have a shot ready for trials in late April, but manufacturing went faster than expected, and by Feb. 24, 42 days after it started, Moderna was shipping the first batch of vaccine to NIAID. After a fast Food and Drug Administration review of the trial plan, the first healthy volunteer was injected on March 16.

BioNTech also started working on a vaccine in January, after Sahin read an article in the *Lancet* describing how the coronavirus had spread in a family that had visited Wuhan. “It showed a pattern which is absolutely critical for a dangerous pandemic disease,” he says. The virus was new, no one was immune, and at least one of the family members hadn’t shown symptoms of infection.

After Sahin discussed the article with Tureci, BioNTech assigned 25 people to start running experiments on mRNA vaccines for the novel coronavirus, setting up shifts that ran through evenings and weekends. By March 2 they’d come up with 20 vaccine candidates that could spur a strong immune response against the virus in lab animals and cell culture

experiments. That day Sahin called Kathrin Jansen, head of vaccine research and development at Pfizer. “We had a very short conversation, and it was very clear that she and her team were very interested,” Sahin says.

The companies started working together almost immediately. They narrowed the field of vaccine candidates to four and on April 23 started testing on people in Germany. A U.S. trial began less than two weeks later. The four options used three different mRNA technologies—BioNTech’s trial, essentially, was a giant scientific experiment to identify the one most likely to make a potent vaccine.

The bragging rights associated with being among the first companies to have vaccines in trials are nice. But with numerous alternatives likely to go into Phase III trials over the next few months, they may not tell us much about the ultimate outcome of the hunt. To the extent that being first matters right now, it’s because of money.

“When these guys put their hands up and said, ‘We’ll be able to go into the clinic in a few weeks,’ you can see why people gave them money,” says Nikolai Petrovsky, a vaccine researcher at Flinders University in Australia. “But it doesn’t mean that they’re the best platform or the most reliable platform or the platforms that will ultimately succeed.” Petrovsky, who founded a small company working on a competing Covid-19 vaccine that uses more established methods, says he hasn’t been particularly impressed by the immune responses generated by mRNA vaccines and worries about how well they’ll be tolerated. He suspects that when all is said and done they’ll prove inferior to vaccines produced using older technologies.

The hype surrounding mRNA vaccines has been lucrative for Moderna’s executives. This year, as share prices have soared on the whole and gyrated wildly on day-to-day vaccine news, Moderna insiders have sold more than \$250 million worth of stock, according to executive compensation data company Equilar Inc. Bancel has sold more than \$18 million since the Covid-19 vaccine program was announced, and investment companies he controls have sold \$11 million more. Moderna says sales by executives are triggered by preexisting share-sales plans, and Bancel says the vast majority of his fortune is still tied up in Moderna stock.



Some scientists were particularly annoyed about a press release on May 18 from Moderna announcing “positive interim clinical data.” Its vaccine had produced neutralizing antibodies in the first eight volunteers, but the company didn’t indicate what kind of numbers those antibodies were being produced in, making it hard to judge how promising the results actually were. Moderna’s shares went up 20% anyway, and the company raised \$1.3 billion in a secondary stock offering later that day.

Bancel says the company decided it had to put out a release because numerous government officials knew the results; it couldn’t take the risk they’d leak. “We were stuck between a rock and a hard place,” he says. When the full trial results were published on July 14, including all the numbers, they confirmed that the vaccine produced antibodies in all people who completed the trial.

Because the coronavirus is a respiratory pathogen that hits many parts of the airway, it’s possible we’ll end up with a partially effective vaccine. That’s as true for mRNA vaccines as for any other approaches, old and new. Patients may have to be revaccinated regularly if the shot’s effectiveness wanes over time. The FDA has indicated it will approve modestly effective vaccines as long as they are safe and prevent the disease or reduce its severity in at least half of those who are vaccinated.

Moderna is planning for success, one way or another. It cut a deal with contract manufacturer Lonza Group AG in May to add manufacturing capacity. Between its plant in Massachusetts and Lonza’s in New Hampshire, Moderna says it hopes to be able to make enough of the vaccine to cover the entire U.S. population. Lonza’s plants in Switzerland have capacity for another 300 million doses. On Aug. 11, Moderna reached a deal to supply 100 million doses of its shot to the U.S. government for up to \$1.5 billion. Pfizer, for its part, has cut a deal to sell 100 million doses of any successful vaccine coming out of its collaboration with BioNTech to the U.S. government for \$1.95 billion. (Moderna’s lower price reflects the government’s financial support of the company’s vaccine development program.)

Bancel says he’s confident Moderna’s vaccine will stimulate antibodies against the coronavirus, as it did in the first patients in the Phase I trial. But whether that prevents people from getting sick, he admits, “we cannot know until we see the Phase III data.” If the trials proceed as fast as Moderna hopes, we may know the answer by late fall.

*(In second-to-last paragraph, updates with news of Moderna’s agreement to sell 100 million doses of its vaccine to the U.S. government.)*

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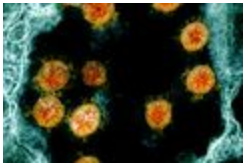
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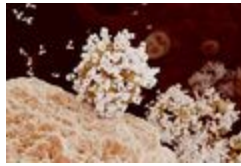
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