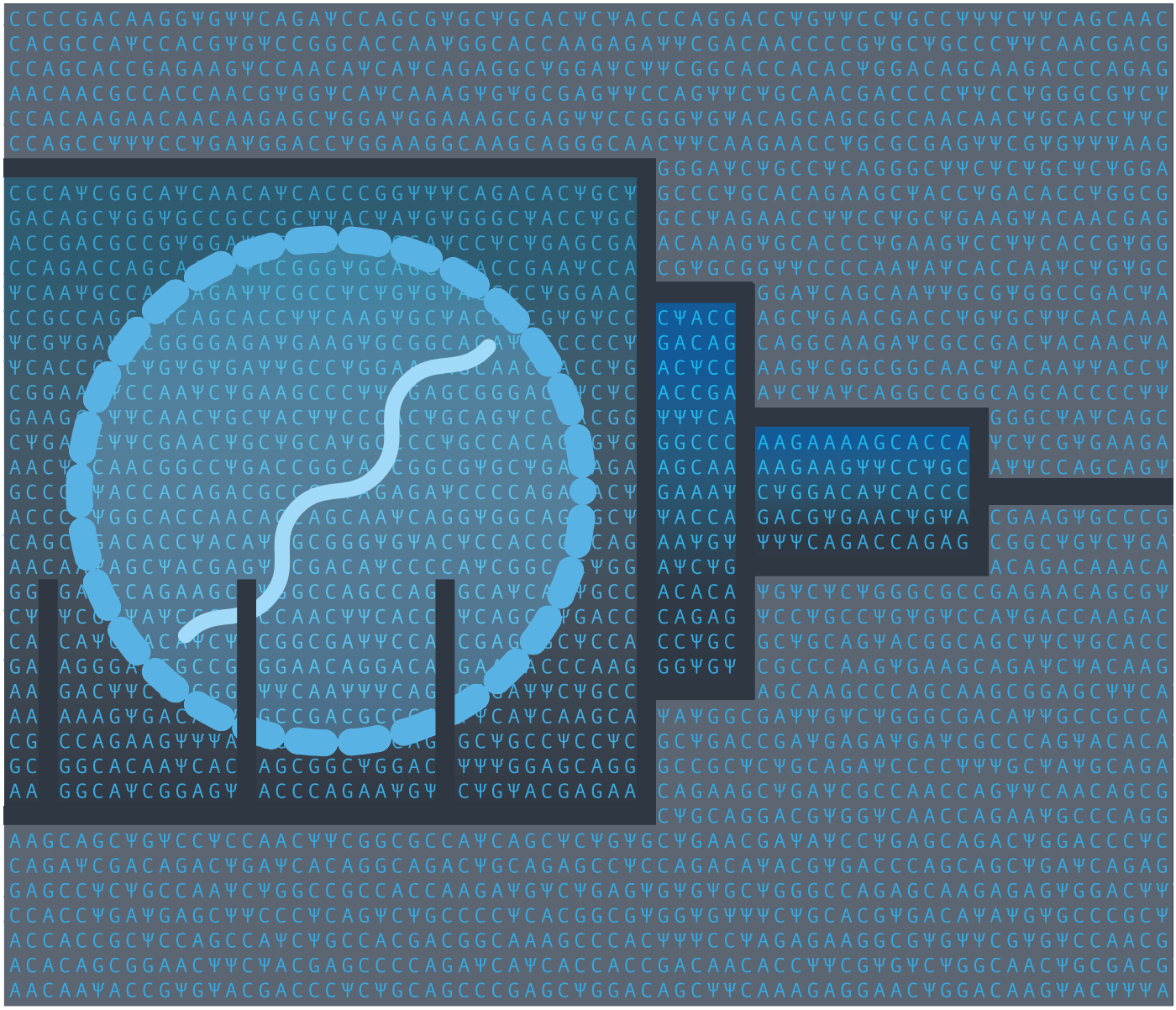


NIK SPENCER/*NATURE*

The RNA sequence used in the COVID-19 vaccine developed by Pfizer and BioNTech (Ψ is a modified form of the uridine nucleotide, U).

THE TANGLED HISTORY OF MRNA VACCINES

Hundreds of scientists had worked on mRNA vaccines for decades before the coronavirus pandemic brought a breakthrough. **By Elie Dolgin**

In late 1987, Robert Malone performed a landmark experiment. He mixed strands of messenger RNA with droplets of fat, to create a kind of molecular stew. Human cells bathed in this genetic gumbo absorbed the mRNA, and began producing proteins from it[1].

Realizing that this discovery might have far-reaching potential in medicine, Malone, a graduate student at the Salk Institute for Biological Studies in La Jolla, California, later jotted down some notes, which he signed and dated. If cells could create proteins from mRNA delivered into them, he wrote on 11 January 1988, it might be possible to "treat RNA as a drug". Another member of the Salk lab signed the notes, too, for posterity. Later that year, Malone's experiments showed that frog embryos absorbed such mRNA[2]. It was the first time anyone had used fatty droplets to ease mRNA's passage into a living organism.

Those experiments were a stepping stone towards two of the most important and profitable vaccines in history: the mRNA-based COVID-19 vaccines given to hundreds of millions of people around the world. Global sales of these are expected to top US$50 billion in 2021 alone.

But the path to success was not direct. For many years after Malone's experiments, which themselves had drawn on the work of other researchers, mRNA was seen as too unstable and expensive to be used as a drug or a vaccine. Dozens of academic labs and companies worked on the idea, struggling with finding the right formula of fats and nucleic acids — the building blocks of mRNA vaccines.

Today's mRNA jabs have innovations that were invented years after Malone's time in the lab, including chemically modified RNA and different types of fat bubble to ferry them into cells (see 'Inside an mRNA COVID vaccine'). Still, Malone, who calls himself the "inventor of mRNA vaccines", thinks his work hasn't been given enough credit. "I've been written out of history," he told *Nature*.

The debate over who deserves credit for pioneering the technology is heating up as awards start rolling out — and the speculation is getting more intense in advance of the Nobel prize announcements next month. But formal prizes restricted to only a few scientists will fail to recognize the many contributors to mRNA's medical development. In reality, the path to mRNA vaccines drew on the work of hundreds of researchers over more than 30 years.

The story illuminates the way that many scientific discoveries become life-changing innovations: with decades of dead ends, rejections and battles over potential profits, but also generosity, curiosity and dogged persistence against scepticism and doubt. "It's a long series of steps," says Paul Krieg, a developmental biologist at the University of Arizona in Tucson, who made his own contribution in the mid-1980s, "and you never know what's going to be useful".

The beginnings of mRNA

Malone's experiments didn't come out of the blue. As far back as 1978, scientists had used fatty membrane structures called liposomes to transport mRNA into mouse[3] and human[4] cells to induce protein expression. The liposomes packaged and protected the mRNA and then fused with cell membranes to deliver the genetic material into cells. These experiments themselves built on years of work with liposomes and with mRNA; both were discovered in the 1960s (see 'The history of mRNA vaccines').

> "RNA in general had a reputation for unbelievable instability."

Back then, however, few researchers were thinking about mRNA as a medical product — not least because there was not yet a way to manufacture the genetic material in a laboratory. Instead, they hoped to use it to interrogate basic molecular processes. Most scientists repurposed mRNA from rabbit blood, cultured mouse cells or some other animal source.

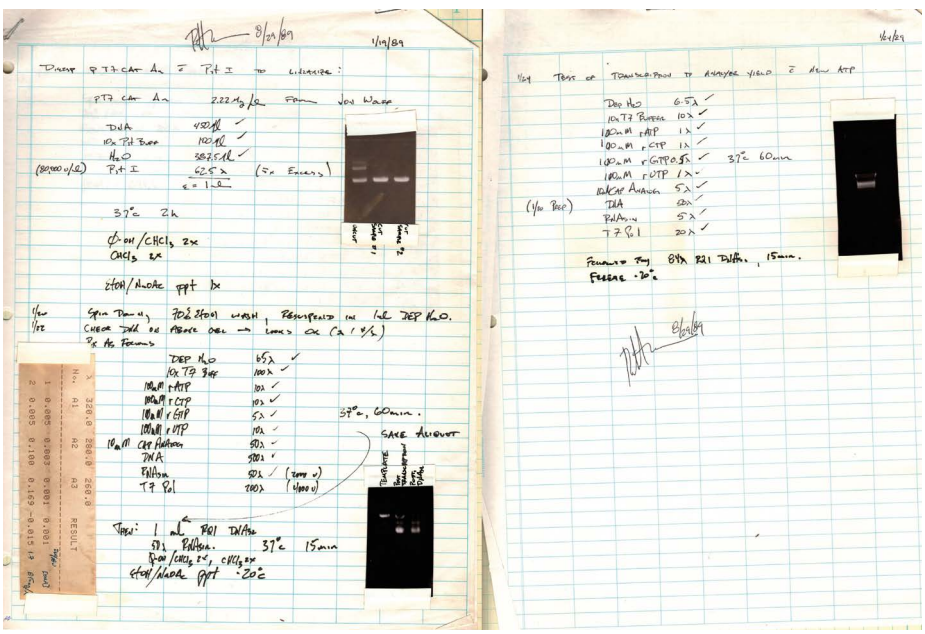
That changed in 1984, when Krieg and other members of a team led by developmental biologist Douglas Melton and molecular biologists Tom Maniatis and Michael Green at Harvard University in Cambridge, Massachusetts, used an RNA-synthesis enzyme (taken from a virus) and other tools to produce biologically active mRNA in the lab[5] — a method that, at its core, remains in use today. Krieg then injected the lab-made mRNA into frog eggs, and showed that it worked just like the real thing[6].

Both Melton and Krieg say they saw synthetic mRNA mainly as a research tool for studying gene function and activity. In 1987, after Melton found that the mRNA could be used both to activate and to prevent protein production, he helped to form a company called Oligogen (later renamed Gilead Sciences in Foster City, California) to explore ways to use synthetic RNA to block the expression of target genes — with an eye to treating disease. Vaccines weren't on the mind of anyone in his lab, or their collaborators.

"RNA in general had a reputation for unbelievable instability," says Krieg. "Everything around RNA was cloaked in caution." That might explain why Harvard's technology-development office elected not to patent the group's RNA-synthesis approach. Instead, the Harvard researchers simply gave their reagents to Promega Corporation, a lab-supplies company in Madison, Wisconsin, which made the RNA-synthesis tools available to researchers. They received modest royalties and a case of Veuve Clicquot Champagne in return.

Patent disputes

Years later, Malone followed the Harvard team's tactics to synthesize mRNA for his experiments. But he added a new kind of liposome, one that carried a positive charge, which



ROBERT MALONE

An excerpt from Robert Malone's lab notebooks, describing the 1989 synthesis of mRNA for injection into mice.

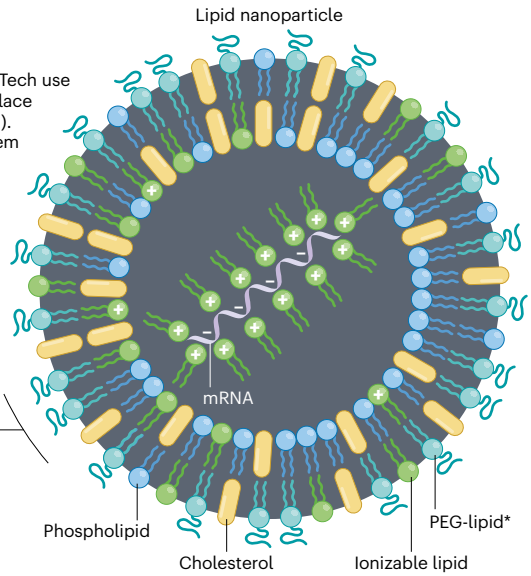
INSIDE AN MRNA COVID VACCINE

COVID-19 vaccines made from messenger RNA use lipid nanoparticles — bubbles of fats — to carry the molecules into cells. The mRNA contains the code for cells to produce the 'spike' protein that the coronavirus SARS-CoV-2 uses to enter cells. Here are key innovations in the design of these vaccines.

The vaccines made by Moderna and Pfizer–BioNTech use mRNA that has been chemically modified to replace the uridine (U) nucleotide with pseudouridine (Ψ). This change is thought to stop the immune system reacting to the introduced mRNA.

To help the body mount an effective immune response to later SARS-CoV-2 infections, the mRNA sequence is adapted to stabilize the spike protein in the shape it uses when fusing with human cells.

The fatty nanoparticle around the mRNA is made of four types of lipid molecule. One of these is 'ionizable': in the vaccine, many of these molecules have a positive charge and cling to negatively charged mRNA, but they lose that charge in the more alkaline conditions of the bloodstream, reducing toxicity in the body.



*Lipid attached to polyethylene glycol

NIK SPENCER/*NATURE*; ADAPTED FROM M. D. BUSCHMANN *ET AL. VACCINES* 9, 65 (2021)

enhanced the material's ability to engage with the negatively charged backbone of mRNA. These liposomes were developed by Philip Felgner, a biochemist who now leads the Vaccine Research and Development Center at the University of California, Irvine.

Despite his success using the liposomes to deliver mRNA into human cells and frog embryos, Malone never earned a PhD. He fell out with his supervisor, Salk gene-therapy researcher Inder Verma and, in 1989, left graduate studies early to work for Felgner at Vical, a recently formed start-up in San Diego, California. There, they and collaborators at the University of Wisconsin–Madison showed that the lipid–mRNA complexes could spur protein production in mice[7].

Then things got messy. Both Vical (with the University of Wisconsin) and the Salk began filing for patents in March 1989. But the Salk soon abandoned its patent claim, and in 1990, Verma joined Vical's advisory board.

Malone contends that Verma and Vical struck a back-room deal so that the relevant intellectual property went to Vical. Malone was listed as one inventor among several, but he no longer stood to profit personally from subsequent licensing deals, as he would have from any Salk-issued patents. Malone's conclusion: "They got rich on the products of my mind."

Verma and Felgner categorically deny Malone's charges. "It's complete nonsense," Verma told *Nature*. The decision to drop the patent application rested with the Salk's technology-transfer office, he says. (Verma resigned from the Salk in 2018, following allegations of sexual harassment, which he continues to deny.)

Malone left Vical in August 1989, citing disagreements with Felgner over "scientific judgment" and "credit for my intellectual contributions". He completed medical school and did a year of clinical training before working in academia, where he tried to continue research on mRNA vaccines but struggled to secure funding. (In 1996, for example, he unsuccessfully applied to a California state research agency for money to develop a mRNA vaccine to combat seasonal coronavirus infections.) Malone focused on DNA vaccines and delivery technologies instead.

In 2001, he moved into commercial work and consulting. And in the past few months, he has started publicly attacking the safety of the mRNA vaccines that his research helped to enable. Malone says, for instance, that proteins produced by vaccines can damage the body's cells and that the risks of vaccination outweigh the benefits for children and young adults — claims that other scientists and health officials have repeatedly refuted.

> "The cost and feasibility of manufacturing just gave us pause."

In 1991, Vical entered into a multimillion-dollar research collaboration and licensing pact with US firm Merck, one of the world's largest vaccine developers. Merck scientists evaluated the mRNA technology in mice with the aim of creating an influenza vaccine, but then abandoned that approach. "The cost and feasibility of manufacturing just gave us pause," says Jeffrey Ulmer, a former Merck scientist who now consults with companies on vaccine-research issues.

Researchers at a small biotech firm in Strasbourg, France, called Transgène, felt the same way. There, in 1993, a team led by Pierre Meulien, working with industrial and academic partners, was the first to show that an mRNA in a liposome could elicit a specific antiviral immune response in mice[8]. (Another exciting advance had come in 1992, when scientists at the Scripps Research Institute in La Jolla used mRNA to replace a deficient protein in rats, to treat a metabolic disorder[9]. But it would take almost two decades before independent labs reported similar success.)

The Transgène researchers patented their invention, and continued to work on mRNA vaccines. But Meulien, who is now head of the Innovative Medicines Initiative, a public–private enterprise based in Brussels, estimated that he needed at least €100 million (US$119 million) to optimize the platform — and he wasn't about to ask his bosses for that much for such a "tricky, high-risk" venture, he says. The patent lapsed after Transgène's parent firm decided to stop paying the fees needed to keep it active.

Meulien's group, like the Merck team, moved to focus instead on DNA vaccines and other vector-based delivery systems. The DNA platform ultimately yielded a few licensed vaccines for veterinary applications — helping, for example, to prevent infections in fish farms. And just last month, regulators in India granted emergency approval to the world's first DNA vaccine for human use, to help ward off COVID-19. But for reasons that are not completely understood, DNA vaccines have been slow to find success in people.

Still, the industry's concerted push around DNA technology has had benefits for RNA vaccines, too, argues Ulmer. From manufacturing considerations and regulatory experience to sequence designs and molecular insights, "many of the things that we learned from DNA could be directly applied to RNA", he says. "It provided the foundation for the success of RNA."

Continuous struggle

In the 1990s and for most of the 2000s, nearly every vaccine company that considered working on mRNA opted to invest its resources elsewhere. The conventional wisdom held that mRNA was too prone to degradation, and its production too expensive. "It was a continuous struggle," says Peter Liljeström, a virologist at the Karolinska Institute in Stockholm, who 30 years ago pioneered a type of 'self-amplifying' RNA vaccine.

"RNA was so hard to work with," says

Matt Winkler, who founded one of the first RNA-focused lab supplies companies, Ambion, in Austin, Texas, in 1989. "If you had asked me back [then] if you could inject RNA into somebody for a vaccine, I would have laughed in your face."

The mRNA vaccine idea had a more favourable reception in oncology circles, albeit as a therapeutic agent, rather than to prevent disease. Beginning with the work of gene therapist David Curiel, several academic scientists and start-up companies explored whether mRNA could be used to combat cancer. If mRNA encoded proteins expressed by cancer cells, the thinking went, then injecting it into the body might train the immune system to attack those cells.

Curiel, now at the Washington University School of Medicine in St Louis, Missouri, had some success in mice[10]. But when he approached Ambion about commercialization opportunities, he says, the firm told him: "We don't see any economic potential in this technology."

Another cancer immunologist had more success, which led to the founding of the first mRNA therapeutics company, in 1997. Eli Gilboa proposed taking immune cells from the blood, and coaxing them to take up synthetic mRNA that encoded tumour proteins. The cells would then be injected back into the body where they could marshal the immune system to attack lurking tumours.

Gilboa and his colleagues at Duke University Medical Center in Durham, North Carolina, demonstrated this in mice[11]. By the late 1990s, academic collaborators had launched human trials, and Gilboa's commercial spin-off, Merix Bioscience (later renamed to Argos Therapeutics and now called CoImmune), soon followed with clinical studies of its own. The approach was looking promising until a few years ago, when a late-stage candidate vaccine failed in a large trial; it has now largely fallen out of fashion.

But Gilboa's work had an important consequence. It inspired the founders of the German firms CureVac and BioNTech — two of the largest mRNA companies in existence today — to begin work on mRNA. Both Ingmar Hoerr, at CureVac, and Uğur Şahin, at BioNTech, told *Nature* that, after learning of what Gilboa had done, they wanted to do the same, but by administering mRNA into the body directly.

"There was a snowball effect," says Gilboa, now at the University of Miami Miller School of Medicine in Florida.

Start-up accelerator

Hoerr was the first to achieve success. While at the University of Tübingen in Germany, he reported in 2000 that direct injections could elicit an immune response in mice[12]. He created CureVac (also based in Tübingen) that year. But few scientists or investors seemed interested. At one conference where Hoerr presented early mouse data, he says, "there was a Nobel prizewinner standing up in the first row saying, 'This is completely shit what you're telling us here — completely shit'." (Hoerr declined to name the Nobel laureate.)

Eventually, money trickled in. And within a few years, human testing began. The company's chief scientific officer at the time, Steve Pascolo, was the first study subject: he injected himself[13] with mRNA and still has match-head-sized white scars on his leg from where a dermatologist took punch biopsies for analysis. A more formal trial, involving tumour-specific mRNA for people with skin cancer, kicked off soon after.

Şahin and his immunologist wife, Özlem Türeci, also began studying mRNA in the late 1990s, but waited longer than Hoerr to start a company. They plugged away at the technology for many years, working at Johannes Gutenberg University Mainz in Germany, earning patents, papers and research grants, before pitching a commercial plan to billionaire investors in 2007. "If it works, it will be ground-breaking," Şahin said. He got €150 million in seed money.

The same year, a fledgling mRNA start-up called RNARx received a more modest sum: $97,396 in small-business grant funding from the US government. The company's founders, biochemist Katalin Karikó and immunologist Drew Weissman, both then at the University of Pennsylvania (UPenn) in Philadelphia, had made what some now say is a key finding: that altering part of the mRNA code helps synthetic mRNA to slip past the cell's innate immune defences.

Fundamental insights

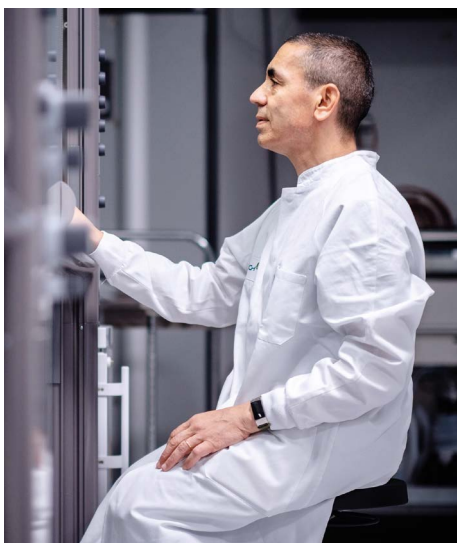
Karikó had toiled in the lab throughout the 1990s with the goal of transforming mRNA into a drug platform, although grant agencies kept turning down her funding applications. In 1995, after repeated rejections, she was given the choice of leaving UPenn or accepting a demotion and pay cut. She opted to stay and continue her dogged pursuit, making improvements to Malone's protocols[14], and managing to induce cells to produce a large and complex protein of therapeutic relevance[15].

In 1997, she began working with Weissman, who had just started a lab at UPenn. Together, they planned to develop an mRNA-based vaccine for HIV/AIDS. But Karikó's mRNAs set off massive inflammatory reactions when they were injected into mice.

She and Weissman soon worked out why: the synthetic mRNA was arousing[16] a series of immune sensors known as Toll-like receptors, which act as first responders to danger signals from pathogens. In 2005, the pair reported that rearranging the chemical bonds on one of mRNA's nucleotides, uridine, to create an analogue called pseudouridine, seemed to stop the body identifying the mRNA as a foe[17].

Few scientists at the time recognized the therapeutic value of these modified nucleotides. But the scientific world soon awoke to their potential. In September 2010, a team led by Derrick Rossi, a stem-cell biologist then at Boston Children's Hospital in Massachusetts, described how modified mRNAs could be used to transform skin cells, first into embryonic-like stem cells and then into contracting muscle tissue[18]. The finding made a splash. Rossi was featured in *Time* magazine as one of 2010's 'people who mattered'. He co-founded a start-up, Moderna in Cambridge.

Moderna tried to license the patents for modified mRNA that UPenn had filed in 2006 for Karikó's and Weissman's invention. But it was too late. After failing to come to a licensing agreement with RNARx, UPenn had opted for a quick payout. In February 2010, it granted exclusive patent rights to a small lab-reagents

Özlem Türeci (left) and Uğur Şahin (right) co-founded the mRNA vaccine firm BioNTech.

BIONTECH SE 2021

HANNAH YOON/BLOOMBERG/GETTY

Katalin Karikó helped to show that chemical modifications to RNA can smuggle the molecule past the body's immune defences.

supplier in Madison. Now called Cellscript, the company paid $300,000 in the deal. It would go on to pull in hundreds of millions of dollars in sublicensing fees from Moderna and BioNTech, the originators of the first mRNA vaccines for COVID-19. Both products contain modified mRNA.

RNARx, meanwhile, used up another $800,000 in small-business grant funding and ceased operations in 2013, around the time that Karikó joined BioNTech (retaining an adjunct appointment at UPenn).

The pseudouridine debate

Researchers still argue over whether Karikó and Weissman's discovery is essential for successful mRNA vaccines. Moderna has always used modified mRNA — its name is a portmanteau of those two words. But some others in the industry have not.

Researchers at the human-genetic-therapies division of the pharmaceutical firm Shire in Lexington, Massachusetts, reasoned that unmodified mRNA could yield a product that was just as effective if the right 'cap' structures were added and all impurities were removed. "It came down to the quality of the RNA," says Michael Heartlein, who led Shire's research effort and continued to advance the technology at Translate Bio in Cambridge, to which Shire later sold its mRNA portfolio. (Shire is now part of the Japanese firm Takeda.)

Although Translate has some human data to suggest its mRNA does not provoke a concerning immune response, its platform remains to be proved clinically: its COVID-19 vaccine candidate is still in early human trials. But French drug giant Sanofi has been convinced of the technology's promise: in August 2021, it announced plans to acquire Translate for $3.2 billion. (Heartlein left last year to found another firm in Waltham, Massachusetts, called Maritime Therapeutics.)

CureVac, meanwhile, has its own immune-mitigation strategy, which involves altering the genetic sequence of the mRNA to minimize the amount of uridine in its vaccines. Twenty years of working on that approach seemed to be bearing fruit, with early trials of the company's experimental vaccines for rabies[19] and COVID-19[20] both proving a success. But in June, data from a later-stage trial showed that CureVac's coronavirus vaccine candidate was much less protective than Moderna's or BioNTech's.

> "The real winner here is modified RNA."

In light of those results, some mRNA experts now consider pseudouridine an essential component of the technology — and so, they say, Karikó's and Weissman's discovery was one of the key enabling contributions that merits recognition and prizes. "The real winner here is modified RNA," says Jake Becraft, co-founder and chief executive of Strand Therapeutics, a Cambridge-based synthetic-biology company working on mRNA-based therapeutics.

Not everyone is so certain. "There are multiple factors that may affect the safety and efficacy of an mRNA vaccine, chemical modification of mRNA is only one of them," says Bo Ying, chief executive of Suzhou Abogen Biosciences, a Chinese company with an mRNA vaccine for COVID-19 now in late-stage clinical testing. (Known as ARCoV, the product uses unmodified mRNA.)

Fat breakthrough

As for linchpin technologies, many experts highlight another innovation that was crucial for mRNA vaccines — one that has nothing to do with the mRNA. It is the tiny fat bubbles known as lipid nanoparticles, or LNPs, that protect the mRNA and shuttle it into cells.

This technology comes from the laboratory of Pieter Cullis, a biochemist at the University of British Columbia in Vancouver, Canada, and several companies that he founded or led. Beginning in the late 1990s, they pioneered LNPs for delivering strands of nucleic acids that silence gene activity. One such treatment, patisiran, is now approved for a rare inherited disease.

After that gene-silencing therapy began to show promise in clinical trials, in 2012, two of Cullis's companies pivoted to explore opportunities for the LNP delivery system in mRNA-based medicines. Acuitas Therapeutics in Vancouver, for example, led by chief executive Thomas Madden, forged partnerships with Weissman's group at UPenn and with several mRNA companies to test different mRNA–LNP formulations. One of these can now be found in the COVID-19 vaccines from BioNTech and CureVac. Moderna's LNP concoction is not much different.

The nanoparticles have a mixture of four fatty molecules: three contribute to structure and stability; the fourth, called an ionizable lipid, is key to the LNP's success. This substance is positively charged under laboratory conditions, which offers similar advantages to the liposomes that Felgner developed and Malone tested in the late 1980s. But the ionizable lipids advanced by Cullis and his commercial partners convert to a neutral charge under physiological conditions such as those in the bloodstream, which limits the toxic effects on the body.

What's more, the four-lipid cocktail allows the product to be stored for longer on the pharmacy shelf and to maintain its stability inside the body, says Ian MacLachlan, a former executive at several Cullis-linked ventures. "It's the whole kit and caboodle that leads to the pharmacology we have now," he says.

By the mid-2000s, a new way to mix and manufacture these nanoparticles had been devised. It involved using a 'T-connector' apparatus, which combines fats (dissolved in alcohol) with nucleic acids (dissolved in an

acidic buffer). When streams of the two solutions merged, the components spontaneously formed densely packed LNPs[21]. It proved to be a more reliable technique than other ways of making mRNA-based medicines.

Once all the pieces came together, "it was like, holy smoke, finally we've got a process we can scale", says Andrew Geall, now chief development officer at Replicate Bioscience in San Diego. Geall led the first team to combine LNPs with an RNA vaccine[22], at Novartis's US hub in Cambridge in 2012. Every mRNA company now uses some variation of this LNP delivery platform and manufacturing system — although who owns the relevant patents remains the subject of legal dispute. Moderna, for example, is locked in a battle with one Cullis-affiliated business — Arbutus Biopharma in Vancouver — over who holds the rights to the LNP technology found in Moderna's COVID-19 jab.

An industry is born

By the late 2000s, several big pharmaceutical companies were entering the mRNA field. In 2008, for example, both Novartis and Shire established mRNA research units — the former (led by Geall) focused on vaccines, the latter (led by Heartlein) on therapeutics. BioNTech launched that year, and other start-ups soon entered the fray, bolstered by a 2012 decision by the US Defense Advanced Research Projects Agency to start funding industry researchers to study RNA vaccines and drugs. Moderna was one of the companies that built on this work and, by 2015, it had raised more than $1 billion on the promise of harnessing mRNA to induce cells in the body to make their own medicines — thereby fixing diseases caused by missing or defective proteins. When that plan faltered, Moderna, led by chief executive Stéphane Bancel, chose to prioritize a less ambitious target: making vaccines.

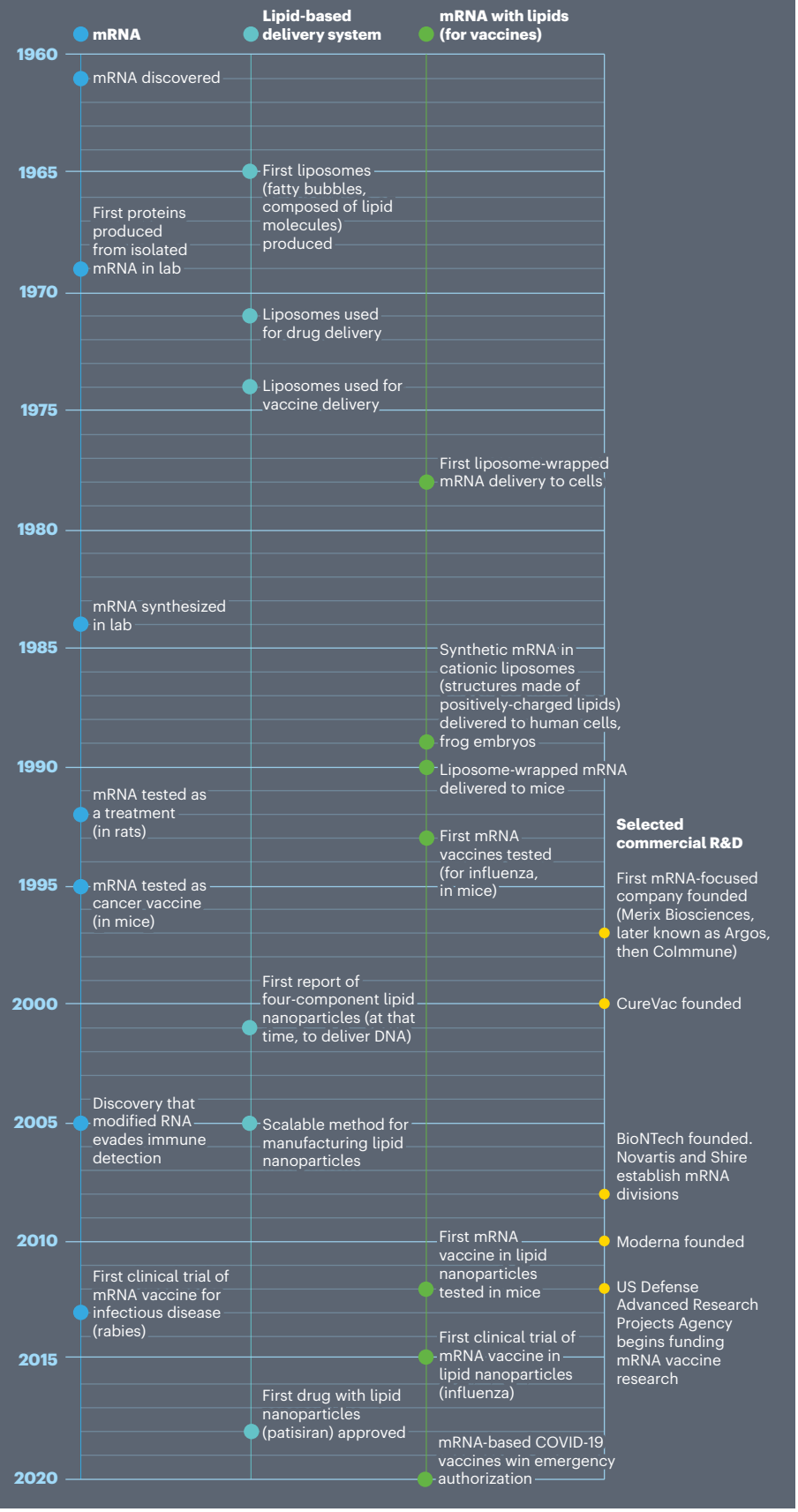
That initially disappointed many investors and onlookers, because a vaccine platform seemed to be less transformative and lucrative. By the beginning of 2020, Moderna had advanced nine mRNA vaccine candidates for infectious diseases into people for testing. None was a slam-dunk success. Just one had progressed to a larger-phase trial.

But when COVID-19 struck, Moderna was quick off the mark, creating a prototype vaccine within days of the virus's genome sequence becoming available online. The company then collaborated with the US National Institute of Allergy and Infectious Diseases (NIAID) to conduct mouse studies and launch human trials, all within less than ten weeks.

BioNTech, too, took an all-hands-on-deck approach. In March 2020, it partnered with New York-based drug company Pfizer, and clinical trials then moved at a record pace, going from first-in-human testing to emergency approval in less than eight months.

THE HISTORY OF MRNA VACCINES

A long chain of scientific advances led to the first messenger RNA (mRNA) vaccines, released last year to protect people against COVID-19. These vaccines, as well as mRNA drugs, make use of developments in the science of mRNA and in delivery systems, which are made of lipid molecules.



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PAUL JOSEPH FOR UBC

Pieter Cullis founded firms that pioneered using lipid nanoparticles to shuttle mRNA into cells.

Both authorized vaccines use modified mRNA formulated in LNPs. Both also contain sequences that encode a form of the SARS-CoV-2 spike protein that adopts a shape more amenable to inducing protective immunity. Many experts say that the protein tweak, devised by NIAID vaccinologist Barney Graham and structural biologists Jason McLellan at the University of Texas at Austin and Andrew Ward at Scripps, is also a prize-worthy contribution, albeit one that is specific to coronavirus vaccines, not mRNA vaccination as a general platform.

Some of the furore in discussions of credit for mRNA discoveries relates to who holds lucrative patents. But much of the foundational intellectual property dates back to claims made in 1989 by Felgner, Malone and their colleagues at Vical (and in 1990 by Liljeström). These had only a 17-year term from the date of issue and so are now in the public domain.

Even the Karikó–Weissman patents, licensed to Cellscript and filed in 2006, will expire in the next five years. Industry insiders say this means that it will soon become very hard to patent broad claims about delivering mRNAs in lipid nanoparticles, although companies can reasonably patent particular sequences of mRNA — a form of the spike protein, say — or proprietary lipid formulations.

Firms are trying. Moderna, the dominant player in the mRNA vaccine field, which has experimental shots in clinical testing for influenza, cytomegalovirus and a range of other infectious diseases, got two patents last year covering the broad use of mRNA to produce secreted proteins. But multiple industry insiders told *Nature* they think these could be challengeable.

"We don't feel there's a lot that is patentable, and certainly not enforceable," says Eric Marcusson, chief scientific officer of Providence Therapeutics, an mRNA vaccines company in Calgary, Canada.

Nobel debate

As for who deserves a Nobel, the names that come up most often in conversation are Karikó and Weissman. The two have already won several prizes, including one of the Breakthrough Prizes (at $3 million, the most lucrative award in science) and Spain's prestigious Princess of Asturias Award for Technical and Scientific Research. Also recognized in the Asturias prize were Felgner, Şahin, Türeci and Rossi, along with Sarah Gilbert, the vaccinologist behind the COVID-19 vaccine developed by the University of Oxford, UK, and the drug firm AstraZeneca, which uses a viral vector instead of mRNA. (Cullis's only recent accolade was a $5,000 founder's award from the Controlled Release Society, a professional organization of scientists who study time-release drugs.)

> **"We're talking hundreds, probably thousands of people who have been working together."**

Some also argue that Karikó should be acknowledged as much for her contributions to the mRNA research community at large as for her discoveries in the lab. "She's not only an incredible scientist, she's just a force in the field," says Anna Blakney, an RNA bioengineer at the University of British Columbia. Blakney gives Karikó credit for offering her a speaking slot at a major conference two years ago, when she was still in a junior postdoc position (and before Blakney co-founded VaxEquity, a vaccine company in Cambridge, UK, focusing on self-amplifying-RNA technology). Karikó "is actively trying to lift other people up in a time when she's been so under-recognized her whole career".

Although some involved in mRNA's development, including Malone, think they deserve more recognition, others are more willing to share the limelight. "You really can't claim credit," says Cullis. When it comes to his lipid delivery system, for instance, "we're talking hundreds, probably thousands of people who have been working together to make these LNP systems so that they're actually ready for prime time."

"Everyone just incrementally added something — including me," says Karikó.

Looking back, many say they're just delighted that mRNA vaccines are making a difference to humanity, and that they might have made a valuable contribution along the road. "It's thrilling for me to see this," says Felgner. "All of the things that we were thinking would happen back then — it's happening now."

Elie Dolgin is a science journalist in Somerville, Massachusetts.

1. Malone, R. W., Felgner, P. L. & Verma, I. M. *Proc. Natl Acad. Sci. USA* **86**, 6077–6081 (1989).
2. Malone, R. W. *Focus* **11**, 61–66 (1989).
3. Dimitriadis, G. J. *Nature* **274**, 923–924 (1978).
4. Ostro, M. J., Giacomoni, D., Lavelle, D., Paxton, W. & Dray, S. *Nature* **274**, 921–923 (1978).
5. Melton, D. A. *et al. Nucleic Acids Res.* **12**, 7035–7056 (1984).
6. Krieg, P. A. & Melton, D. A. *Nucleic Acids Res.* **12**, 7057–7070 (1984).
7. Wolff, J. A. *et al. Science* **247**, 1465–1468 (1990).
8. Martinon, F. *et al. Eur. J. Immunol.* **23**, 1719–1722 (1993).
9. Jirikowski, G. F., Sanna, P. P., Maciejewski-Lenoir, D. & Bloom, F. E. *Science* **255**, 996–998 (1992).
10. Conry, R. M. *et al. Cancer Res.* **55**, 1397–1400 (1995).
11. Boczkowski, D., Nair, S. K., Snyder, D. & Gilboa, E. *J. Exp. Med.* **184**, 465–472 (1996).
12. Hoerr, I., Obst, R., Rammensee, H. G. & Jung, G. *Eur. J. Immunol.* **30**, 1–7 (2000).
13. Probst, J. *et al. Gene Ther.* **14**, 1175–1180 (2007).
14. Karikó, K., Kuo, A., Barnathan, E. S. & Langer, D. J. *Biochim. Biophys. Acta* **1369**, 320–334 (1998).
15. Karikó, K., Kuo, A. & Barnathan, E. *Gene Ther.* **6**, 1092–1100 (1999).
16. Karikó, K., Ni, H., Capodici, J., Lamphier, M. & Weissman, D. *J. Biol. Chem.* **279**, 12542–12550 (2004).
17. Karikó, K., Buckstein, M., Ni, H. & Weissman, D. *Immunity* **23**, 165–175 (2005).
18. Warren, L. *et al. Cell Stem Cell* **7**, 618–630 (2010).
19. Aldrich, C. *et al. Vaccine* **39**, 1310–1318 (2021).
20. Kremsner, P. G. *et al. Wien. Klin. Wochenschr.* https://doi.org/10.1007/s00508-021-01922-y (2021).
21. Jeffs, L. B. *et al. Pharm. Res.* **22**, 362–372 (2005).
22. Geall, A. J. *et al. Proc. Natl Acad. Sci. USA* **109**, 14604–14609 (2012).