# Introduction: What Happens When the Jab Goes into Your Arm?

If you're living in the United States or Europe, chances are high you have been vaccinated against COVID-19 with an mRNA vaccine—along with billions around the world.

Questions and sometimes cultural resistance against these new types of vaccines have largely resulted from the apparent speed at which they were developed—well under a year between the sequencing of the coronavirus in China and the approval of the first mRNA vaccines in the United States. Typically, it takes 10 years to develop a vaccine. More than 80 new viruses have been identified since 1980, but only three new vaccines have been developed in that time. This leads to another question: Why were these RNA vaccines generated by companies unknown to all but a few smart investors?

## Unanswered Questions

By February 2021, after 1 year of COVID-19 coverage and some rapid brushing up of my molecular biology, I still had no tidy answers to these questions. What was clear to me, though, was that the knowledge, technology, and know-how required to bring mRNA vaccines to market could not possibly have been acquired in only 10 months. So I started to dig deeper. Finding only snippets of information and summaries, I decided to trace the history of the RNA vaccines by talking to the individuals involved in this amazing collective 30-year enterprise. This investigation reveals the story of RNA research that made the first COVID-19 vaccines possible and opened a new medical revolution. Because make no mistake: COVID-19 is the first disease for which severe consequences became preventable thanks to mRNA-based technology. With more than 400 clinical trials against various viruses as well as against cancers and other diseases, mRNA is now ushering in a new era in medicine.

Dozens of interviews, mostly conducted via Zoom with scientists in their laboratories or offices at universities in the United States, Germany, France, and Switzerland, revealed a great deal—not least that there was no single parent behind the development of mRNA as a therapeutic tool. It was a collective enterprise between people who were often as close as family. And as with any family, there were arguments, doubts, jealousy, and mistakes, leaving a legacy of disputes, many surrounding patenting issues.

## Future Nobel Laureates

These researchers were mostly molecular biology outsiders—albeit a few already with Nobel Prizes and with more surely destined to become future laureates. The majority, however, suffered the skepticism of their peers, seeing their articles rejected by prestigious journals and their studies snubbed by the pharmaceutical industry. Some have forfeited their careers, others millions of dollars.

The international triumph of mRNA vaccines against COVID-19 has clearly changed the fortunes of many in a field now attracting talents and money. The medical revolution heralded by RNA-related technologies extends well beyond vaccines, to treatments for cancer, heart disorders, autoimmune diseases such as multiple sclerosis, and hereditary conditions like cystic fibrosis. It's a medical gold mine and one likely to prove a fierce battleground of intellectual property.

Before launching into the detail of mRNA's development as a therapy, it's important to first consider the fundamental science behind it—starting with what happens when the vaccine is injected into the upper arm.

## The Spatial Beauty of Calder and Tinguely

To my mind, the process has a spatial beauty reminiscent of the slightly ironic cascading logic of Jean Tinguely's machines and the fragile equilibrium of Alexander Calder's mobiles. Messenger RNA is a monument of Darwinian evolution. Messenger RNA converts the information contained in DNA—the molecule found in every cell and that holds the genetic blueprint for nearly everything that constitutes life—into the myriad proteins that govern the functioning of our cells and, in turn, that of our tissue and organs.

Proteins are responsible for most of what goes on inside our bodies. They carry oxygen and nutrients. They produce movement and signals. And they sound the alarm, detecting alien invaders such as viruses and calling up the body's defenses. This is the principle behind vaccination—vaccines hack the immune system by imitating a benign attack. A conventional vaccine is a virus that has been neutralized or killed; when meeting it in this benign form, the immune system learns to recognize and tackle the foreign agent without being put at risk.

## Computer Games in the Body

Dietmar Hopp, the founder of German tech giant SAP, and Bill Gates are both said to see mRNA as a type of biological software, a program that can be coded. If that's the case, a good metaphor for how an mRNA vaccine works might be something like the video game *Grand Theft Auto*.

The hero of the game is a mail carrier (mRNA). The challenge is to deliver a blueprint to a workshop, for the creation of a molecule capable of detecting COVID-19. This blueprint is in the form of a tattoo—a 4000-character sequence containing only four letters. The mail carrier has an official cap for identification purposes and a special uniform. The house (or cell) to which the blueprint must be delivered is in a dodgy neighborhood bristling with 300 species of watchdog (the different ribonucleases) whose instinct is to go for the kill.

If the mail carrier makes it to the destination—which isn't always the case, so these vaccines contain millions of mRNA mail carriers—then the special uniform changes color (in reality, it changes electrical charge—a miracle of bioengineering, as we shall see) to open the door. But the job isn't finished yet.

Plenty of dangers lie in wait for our mail carrier inside the house (the cell) too. More killer watchdogs (cytokines) are lurking, but those clever tattoos help give them the slip. The dogs bark, alerting the immune system's police, but they don't bite yet. When he reaches the workshop (the ribosomes), our mail carrier's cap acts as the password.

Now, the assembled blueprint is used as a "wanted" notice and stuck up in the windows of the house. This alert is like an identikit image of the coronavirus for the police (the immune system). Should the coronavirus

appear, the police can send out their Alsatians (antibodies) and snipers (T-lymphocytes) to deal with it. But nature is unforgiving. Once the mail carrier has completed the mission, the dogs make their kill. You, on the other hand, are protected.

This investigation tells the story of 30 years of research and technological development, mapping out the creation of this vaccine. (Along with many other therapies, now in the making.) It's a tale of scientific obstacles, epic patent battles, and surviving the scorn of researchers obsessed with a different molecule: DNA. And then there's the skepticism of big pharma, which, until it proved itself during the pandemic, remained largely impervious to mRNA's therapeutic potential.

Moroccan-born scientist Professor Moncef Slaoui watched how mRNA technology gave birth to the first approved COVID-19 vaccines from a privileged seat, as scientific head of President Donald Trump's Operation Warp Speed from May 2020. He will tell us what it was like working on the inside.

## Stumbles in the Final Straight

Since the very first vaccine, the adoption of technology intended to protect people in good health, rather than to cure sick patients, into mainstream medicine has been slow. Edward Jenner, the eighteenth-century inventor of vaccination, was forced to self-publish his experiments on smallpox because the Royal Society didn't dare, for fear of harming its reputation.

So Slaoui was unsurprised at how long it had taken for mRNA technology to be adopted. "Vaccines are injected into healthy people, so it takes an emergency like a pandemic to be able to introduce new vaccine technology."

# 1960–1990: The Beatles Years of mRNA

Fundamental research that took place between 1960 and 1990 solved the mystery of *how* RNA made the crucial step between DNA and the proteins it coded.

The period created fertile conditions for the next phase, during which scientific understanding and the newly developed technologies could be applied to medicine. As ever, it was pure research that led the way. Tom Cech, 1989 Nobel laureate in chemistry and heavily involved in this research, says, "What motivated us at first was not the medical applications. It was to understand the mechanisms of life."

Biologist James Darnell gave a detailed insider's account of these early days in his 2011 book *RNA: Life's Indispensable Molecule*. As he explains, the whole enterprise was sparked by questions springing from British researchers at the University of Cambridge. Fred Sanger (winner of Nobel Prizes in 1958 and 1980) showed through his 1951 sequencing of insulin that proteins are arranged in molecular building blocks—in the form of 20 amino acids—uniquely ordered. Soon after, in 1953, James Watson and Francis Crick, the 1962 Nobel laureates, proved with their description of DNA's double-helix structure that the information on which all life is based is also organized in a specific way.

## Proof That Messenger RNA Exists

The question arising from these discoveries asked where these sequences interact and how genetic information is transferred and transcribed into the proteins that shape cells and fulfill the thousands of essential functions of life.

In the 1950s, transfer RNA was discovered. This kind of RNA transports amino acids so that they can be incorporated as proteins by tiny

synthesis factories: ribosomes. An article postulating the existence of messenger RNA (mRNA) in 1961, and the publication of proof by François Jacob, Jacques Monod, and Sydney Brenner the following year, boosted research immensely. The missing link between DNA and proteins had been found. But this still did not explain *why* a cell chooses a particular protein and *how* it produces it.

In the 1960s, U.S. biochemists (including Marshall Nirenberg, Severo Ochoa, and Gobind Khorana) explained for the first time how information is organized within RNA. They showed that the four bases of RNA—the nucleosides A, C, G, and U, equivalent to DNA's four nucleotides A, C, G, and T—combine to form sequences of triplets called codons—for instance, AUA, GCC, and so on, in 64 possible combinations. It is the arrangement of these codons—RNA's code words—that determines how the 20 amino acids are organized and how it gives different proteins their specific properties. As scientists' knowledge of these structures deepened, they began to understand the mechanism by which DNA's code of life is transcribed into the proteins that shape existence. This is how we came to understand the role of mRNA.

## A Wave of Seminal Discoveries

These discoveries triggered a multitude of research projects. Bacteria was the subject of the first experiments in the late 1960s: an easy starting point with only 2000 to 3000 different proteins, compared with tens or even hundreds of thousands in the human body. But during the 1970s, research increasingly focused on RNAs in more complex organisms, leading to a further wave of seminal discoveries.

Biologists Mary Edmonds (University of Pittsburgh) and Aaron Shatkin (Rutgers University in New Jersey) identified the structures that finish and cap mRNA. These are essential to protecting mRNA and connecting it to ribosomes, as well as differentiating it from other types of RNA. As the 1980s dawned, Tom Cech (University of Colorado) and Phillip Sharp (MIT) showed how RNA derived from DNA specializes to produce a plethora of proteins. Their work earned each of them a Nobel Prize, in 1989 and 1993, respectively.

## The Magic of the Molecule

"This is the magic of the molecule," Cech says from his office at the University of Colorado in Boulder with its view of the Rockies. "It is both a vector of information and the matrix of functions, of chemical catalysis."

On a Zoom call from his office in MIT, Sharp explains that although these discoveries have not fed directly into the current vaccines, they did make them possible. "It is this knowledge that will, for example, help determine the optimal organization of codons in the spike protein expressed by the vaccines."

Cech adds, "This quest for knowledge was also at the origin of the artificial RNA synthesis technologies that are the basis of those used today." In 1984, a team of developmental and molecular biologists led by Paul Krieg and Douglas Melton at Harvard University developed the method to synthetize and copy/paste active mRNA with an enzyme they took from a virus.

These fundamental research projects also identified the 300 or so enzymes (the watchdogs from our earlier metaphor) that work to break down mRNA in our bodies, either because it has outlived its use or because it has been identified as an alien invader—a virus, for instance. These enzymes give the mRNA molecule its "almost mythical reputation for instability," according to Juan Valcárcel Juárez, a Spanish biologist and former president of the RNA Society.

## Skepticism and Mockery from Peers

RNA's reputation for instability had a considerable impact on future research. Its cousin DNA, which was seen as stable, attracted significant interest from both researchers and funders. The first recombinant molecules were produced by genetic engineering in 1975, opening the era of biological drugs developed by biotech companies such as Genentech, Amgen, and Biogen. In contrast, by the late 1980s, not a single laboratory worldwide had yet discovered an RNA-based therapy.

For the next 30 years, the pioneers of mRNA technology battled against its presumed instability. Many biologists and pharma managers looked on with skepticism and mockery at its therapeutic potential—until the advent of vaccines against COVID-19 conclusively proved the case for mRNA.