- Vaccination / COVID-19

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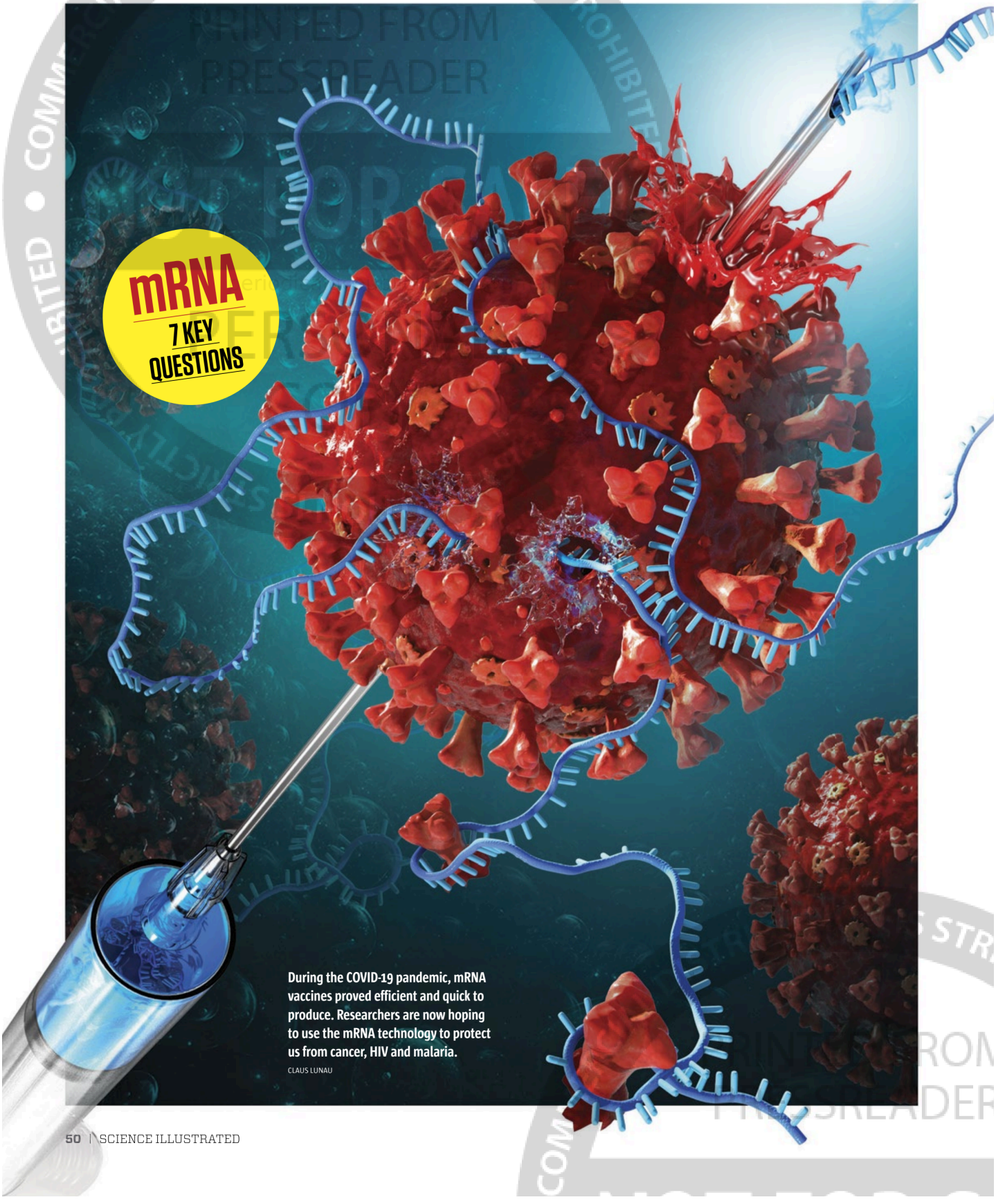
mRNA
7 KEY QUESTIONS



During the COVID-19 pandemic, mRNA vaccines proved efficient and quick to produce. Researchers are now hoping to use the mRNA technology to protect us from cancer, HIV and malaria.

CLAUS LUNAU

By **Inge Revsbech**

7 things you need to know about mRNA and

mRNA vaccines' next trick

mRNA vaccines have proven a medical breakthrough in turning the body's own cells into drug factories. And the fight against COVID-19 may have been just the first battle that mRNA vaccines will help us win. Researchers are now developing mRNA vaccines to work against other deadly diseases.

Quick guide to mRNA

WHY WE TALK ABOUT IT

mRNA vaccines are more efficient and can be cheaper than traditional vaccines.

WHAT DOES IT MEAN?

The 'm' in mRNA stands for 'messenger' – of a 'recipe' carried into the body cells to produce antigens of a particular disease.

VAST NUMBERS

As of 3 January 2024, 13.5 billion COVID-19 vaccine doses had been administered worldwide. Not enough countries report vaccine type for full figures of mRNA vaccines, but Pfizer-BioNTech alone has manufactured at least 4.6 billion doses.

The death toll from COVID-19 was large, with the estimates of excess deaths ranging from three million to 15 million and up. It made millions more seriously ill, and caused economic shut-downs that nevertheless allowed the rich to get richer and left the poor getting poorer.

Few good things came out of the global pandemic. But perhaps mRNA vaccines will prove to be one of them.

During the pandemic, researchers and authorities worked together, racing to finalise the development of this extremely potent new type of vaccine. Unlike other vaccines, mRNA vaccines are not based on microorganisms or parts taken from the real disease. Instead mRNA vaccines are 100% artificial, making them more efficient and faster to manufacture.

How does a vaccine work?

Vaccines teach your immune system to fight disease without you having to get sick first. With traditional vaccines, a weakened version of disease-causing bacteria or viruses is injected into the body, which recognises them as foreign bodies through the unknown proteins they bring. These 'markers' or 'antigens' tell your immune system whether something in your body is harmful or not.

When the body's immune system recognises an antigen, it is put on the death list and the immune system's B cells (a type of white blood cell) produce special antibodies to bind to the antigen. These antibodies then act as markers for the immune system's death squad, macrophages, to find. Their job is to destroy the cells or microorganisms that have been labelled by the B cells.

To prepare the body for the next attack, some of the B cells produce 'memory cells' that will remember the antigen to speed up the response if the same microorganisms attack again. The immune system also activates several types of T cells (other white blood cells), which both boost the immune response and kill infected cells.

What is an mRNA vaccine?

An mRNA vaccine is different – it contains no viruses, bacteria or antigens. The 'm' is short for 'messenger': mRNA is a small copy of a piece of DNA that contains code for specific proteins.

This mRNA finds its way into our cell protein factories: ribosomes. There they instruct cells to build whichever protein is in the mRNA's recipe. Artificial mRNA vaccines bring a recipe for an infection's antigens (the proteins that mark the disease), making the ribosomes build the hostile (but harmless alone) antigens.

Once the antigens are produced in the body, the immune response operates in a similar way to traditional vaccines: the immune system attacks the antigens and remembers them, if they reappear. The patient has now been vaccinated.

The COVID-19 vaccines from Moderna and Pfizer-BioNTech were the first mRNA vaccines to be approved. Both contained mRNA that held the recipe for a specific antigen – a spike protein that formed part of the surface of the virus.

How does mRNA get to a cell?

In theory the behaviour of mRNA is simple, but getting it to work was not easy for researchers, especially as mRNA is rapidly broken down in the body and falls apart very easily.

This problem was overcome by hiding the mRNA vaccine in a lump of fat. And by using a small bubble of fat resembling the surface of a specific cell type, the fat can not only hold the mRNA together, it can sneak the mRNA into our cells.

The COVID-19 vaccines used mRNA fat bubbles resembling the surface of dendritic immune cells – messengers that process antigen material and present it on the cell surface of T cells. By presenting the mRNA in a similar form, its fat bubbles are able to bind to these cells, and the mRNA gains direct access to the cell.

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PEGGY PETERSON/UNIVERSITY OF PENNSYLVANIA

Katalin Karikó and Drew Weissman were awarded the 2023 Nobel Prize in Physiology or Medicine for their research into mRNA vaccines. Their work in making mRNA vaccines appear more 'natural' to the body's defence systems enabled the rapid production of efficient vaccines against COVID-19.

Who invented mRNA vaccines?

The potential of mRNA was realised in 1989, when American biochemist Robert Malone had a brilliant idea. Mixing fat and mRNA with mouse cells, Malone induced transfection – the artificial introduction of nucleic acids (DNA or RNA) into the mouse cells.

In Malone's experiment, the proof of transfection was that the mouse cells became luminous, because the mRNA carried the recipe for luciferase, an enzyme that allows the production of light, as known from fireflies, luminous jellyfish, plankton and fungi.

Then later, researchers discovered that the mRNA inside its fat bubble could also carry the recipe for a virus antigen – and hence activate the immune system.

But it was still not straightforward. One factor caused problems: the initial building blocks of the artificial mRNA were too 'pure'; the immune system realised something was wrong and attacked it. In 2005, however, they managed to modify mRNA to look exactly like something the body could have made itself. And this breakthrough proved crucial in 2020, when researchers needed to quickly produce an efficient vaccine against COVID-19.

So it was this discovery – the modification of nucleoside bases to deliver more natural-looking mRNA – that won the 2023 Nobel Prize in Physiology or Medicine for the team of researchers from the University of Pennsylvania in the US, led by Katalin Karikó and Drew Weissman.

Which vaccines use mRNA?

Before the COVID-19 pandemic, several mRNA vaccines were tested, but none had yet been approved.

However, the groundwork meant that when the pandemic struck, drugmakers were able to finalise a design and begin production of COVID-19 vaccines at an unprecedented pace.

Moderna claims to have designed its mRNA vaccine in just two days, and with active support of regulators and the overlapping of normally separate trials, it was possible to produce, test, and approve new mRNA vaccines in just a few months – a process that normally takes years. Today, the COVID-19 vaccines from Moderna and Pfizer-BioNTech remain the only approved mRNA vaccines – but they have been administered in billions of doses.

4,600,000,000

doses of mRNA vaccine against COVID-19 have been produced by Pfizer-BioNTech.

What else can mRNA do?

mRNA technology research has only just begun. Researchers are developing other vaccines, and right now the main focus is on vaccines against cancer. The immune system's T cells are responsible for killing infected cancer cells, and via the production of specific antigens, mRNA technology could give them an advantage in the fight.

Others targets for mRNA vaccines include HIV, malaria, rabies, influenza, Zika and tuberculosis. The potential of mRNA technology is huge, and a number of research projects are very promising. But approved mRNA treatments for other illnesses will be years away – partly because the rapid trials and approvals allowed by authorities during the COVID-19 vaccine development will not carry over into ongoing drug development.

Are mRNA vaccines better than other vaccines?

mRNA vaccines have advantages, as well as possible disadvantages. The resulting antigen alone might spur less protection than the whole or part virus included in traditional vaccines. Yet the COVID-19 mRNA vaccines were judged to provide 60-90% protection against the variants of the disease. A regular flu vaccine's percentage success is only 30-60%.

In addition, by using nothing of the original disease-causing organism, mRNA ensures that patients cannot possibly contract the disease, as can happen in traditional vaccination.

Stability is another disadvantage: the easy breakdown of mRNA requires such vaccines to be stored at low temperatures, which could limit distribution in hot countries. And like all vaccines there can be side-effects, with the added issue that we still lack long-term data on those side-effects from mRNA vaccines.

In the plus column, mRNA vaccines are simpler to design and manufacture. The production apparatus and chain is shorter and more time-efficient than for traditional vaccines, because drug companies do not have to carefully control the production of weakened microorganisms or their antigens in a lengthy lab process. Instead, the recipe, mRNA, is simply given to the body, and the body's cells are quite efficient at producing it themselves.

So while flu vaccines take 5-6 months to produce, and polio vaccines 18 months. Pfizer-BioNTech's COVID-19 vaccine can now be produced in just 60 days. SI

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mRNA prepares the immune system for battle

A vaccine protects you against viruses by teaching the immune system to recognise and attack the virus. The new mRNA vaccines achieve this through the DNA-like substance of RNA, which makes your cells produce only the virus' proteins.

mRNA is similar to DNA, but with only a single strand of bases.

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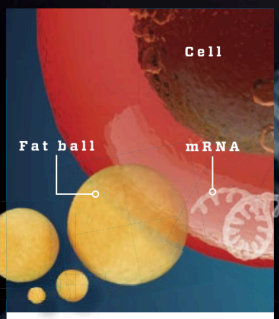
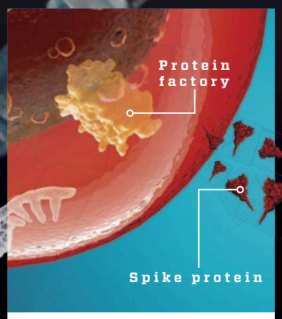


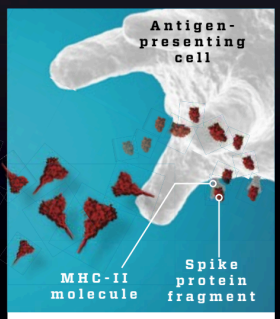
Fat balls deliver mRNA to cells

1 Scientists produce mRNA (white) with genetic instructions to build the spike protein of the coronavirus. The mRNA is embedded in fat balls (orange) and injected into the body. Subsequently, the fat balls deliver the mRNA to cell interiors.



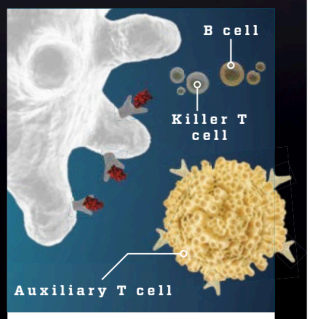
Cells build virus protein

2 Your cells normally use mRNA created from the genes in your DNA to build proteins. The vaccine utilises this machinery (yellow) to build spike proteins (red triangles). The newly-built proteins are secreted into the bloodstream.



Immune cells cut protein to pieces

3 The spike proteins are absorbed by immune system cells known as antigen-presenting cells (white). They break down the protein into small fragments that attach to MHC-II molecules (grey) on the surface of immune cells.



The immune system prepares for attack

4 The immune system's auxiliary T cells (light yellow) bind to the fragments and then activate other immune cells (yellow and green) including B cells, which produce antibodies against the virus, and killer T cells that kill infected cells.

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