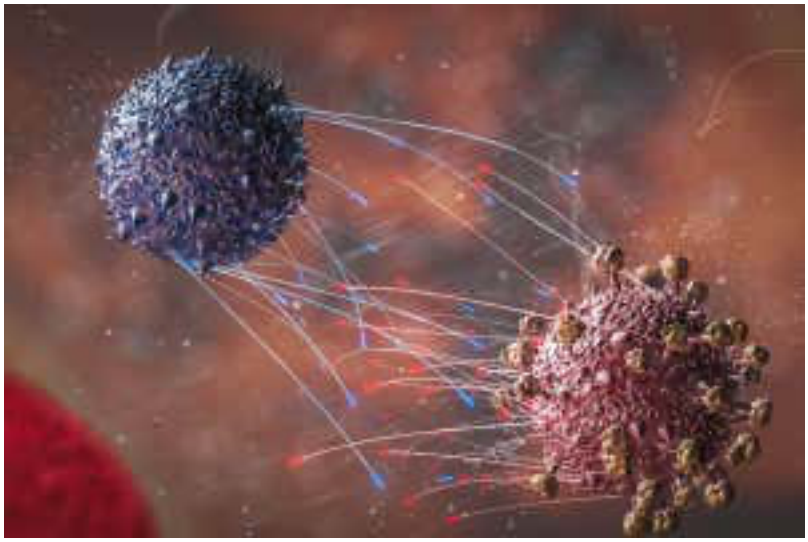
What are mRNA vaccines and how useful will they be?



An artist's representation of a T-cell (blue) attacking the new coronavirus

A collective wave of excitement swept around the world when Pfizer and BioNTech announced positive early results from their coronavirus vaccine trial last week. Now, biotechnology firm Moderna has announced even better findings. These are no ordinary vaccines: they could be the first messenger RNA (mRNA) vaccines to be approved. If this technology lives up to its promise, it could bring huge benefits for healthcare, not just for tackling the coronavirus.

"Part of the reason why the results from Pfizer are so exciting is that nobody has ever shown in humans that an mRNA vaccine can be effective," says Anna Blakney at Imperial College London, who is working on a different vaccine. "I think it will change the way we make a lot of vaccines."

Viruses consist of the recipe for making more viruses wrapped in a protein coat. Our immune system fights them by learning to recognise that outer protein.

Almost all vaccines physically contain such a viral protein in some form. Many vaccines contain entire viruses, coat proteins and all, using either harmless strains of dangerous viruses or inactivated viruses. Some more modern ones, called subunit vaccines, just contain the outer protein.

"**100x**
As many doses can be made with self-amplifying vaccines from the same amount of mRNA"

All of these vaccines are tricky to develop and manufacture, not least because viruses and proteins can only be made in living cells. Flu vaccines are typically grown in chicken eggs, for instance.

By contrast, mRNA vaccines contain the instructions for making the viral protein instead of the protein itself. mRNAs are an essential part of cellular biology – they are copies of the genes in our genome and act as a template for making proteins. If mRNAs that code for a viral gene are added to a human cell, the cell will start making that viral protein and continue to make it for several weeks until the mRNAs break down. Because only the outer protein is made, not the whole virus, there is no chance of an actual infection.

Some of the viral proteins stick out from the membrane of the cell, where they are spotted by immune cells. This triggers the production of antibodies. Their role is to bind to matching viruses and stop them entering cells.

Crucially, the protruding proteins also stimulate the production of T-cells that detect infected cells. Destroying infected cells prevents more viruses being released. A strong T-cell response is thought be crucial for immunity to the coronavirus, but not all vaccines produce one.

Perhaps the biggest advantage of mRNA vaccines is that they can be developed and manufactured quickly once the genome of a virus has been sequenced. Moderna started testing its mRNA vaccine in people just 66 days after the coronavirus was sequenced.

This speed is obviously a huge advantage when new viruses emerge. It also means that if, say, the virus mutated in a way that made vaccines less effective, any mRNA vaccine could be quickly altered by tweaking the sequence.

The big obstacle to mRNA vaccines until recently has been delivery. If you simply inject mRNAs into someone's arm, they are quickly chewed up by enzymes in the blood.

One way to solve this is to deliver the gene for the viral protein inside the empty shell of a harmless virus, which is the basis of several potential coronavirus vaccines. With vaccines like Pfizer's and Moderna's, the mRNAs are packaged in tiny droplets of fat called lipid nanoparticles, which protect them and help them get into cells.

Some mRNA vaccines, such as the one being developed at Imperial College London, use a trick that further speeds up manufacture. This vaccine is "self amplifying". It consists of a longer piece of mRNA that also codes for enzymes that encourage cells to make more copies of the mRNA, so more viral proteins are produced. With a self-amplifying vaccine, 100 times as many doses can typically be made from the same amount of mRNAs.

"Obviously, that's really important with a global pandemic where you're trying to produce billions of doses of a vaccine," says Blakney.

If other mRNA vaccines prove to be as effective, they could be used to prevent many other diseases, from herpes to flu. They also show promise as a way of treating cancers. Tumour cells often make mutant proteins. These can be found by sequencing the genome of cancer cells, and a personalised mRNA vaccine can then be made.

Yet it is still early days. Both the Pfizer and Moderna results are just interim analyses, so we will have to wait to see whether mRNA vaccines deliver on the shot of optimism they have promised.