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The future of medicine unlocked

When the covid-19 pandemic finally showcased the power of mRNA therapies, it opened the door to a medical revolution, finds Michael Le Page

Viruses may be our enemies, but they have taught us a thing or two. When a virus takes hold, it hijacks our cells and puts them to work churning out the materials to make more virus. It is a diabolically effective strategy, allowing these invaders to rapidly grow their forces and get the jump on our immune systems.

The thing is, if they can commandeer our cells’ protein-making factories for their own ends, why can’t we do the same to bolster our defences? We can, it turns out. This was the insight that set in motion decades of research that culminated in the Pfizer/BioNTech and Moderna vaccines against covid-19: they use the genetic material messenger RNA to tell our cells to produce a protein that teaches our bodies to recognise the invaders.

The pandemic has been a proving ground for this technique, spectacularly demonstrating how rapid – and potentially cheap – it can be. “The covid vaccines really illustrate how quickly one can develop these medicines,” says Pieter Cullis at the University of British Columbia in Canada. “From a standing start you saw things being in the clinic in three months.”

Vaccines are only the beginning. If we can recruit our bodies to make medicines this way, that opens the door to treating everything from bacterial infections to autoimmune conditions, rare genetic disorders and cancer. “It is a revolution in terms of the medicines you can imagine, and also produce and test very quickly,” says Cullis. It is early days yet, even if promising results are already coming in. And yet it is no exaggeration to say that this could change everything.

To grasp why there is so much excitement about the potential of mRNA vaccines and related treatments, we need to go back a bit. Early vaccines consisted of “live” viruses, typically with mutations that make them less dangerous than the wild virus they protect against. Live vaccines can be very effective, but have drawbacks: they are tricky to make, because viruses can only be produced by living cells, and they can be a threat to people with weakened immune systems. What’s more, live vaccine viruses sometimes mutate back into a dangerous form, as happens occasionally with the live polio vaccine.

This is why many modern vaccines consist of “dead” or inactivated viruses, or even just one isolated protein from a virus, in the case of subunit vaccines. But these aren’t any easier to make: any protein-based medicine still has to be produced in living cells.

This requirement is an issue at every stage of traditional vaccine development, from preparing doses for initial tests to mass manufacturing. It also makes it hard to tweak candidate vaccines if they don’t work well.

But many decades ago, biologists realised there is a potential shortcut: instead of injecting the virus or its proteins, give our
bodies the genetic recipes for making viral proteins. Recipes for proteins are usually permanently stored in the DNA in the nucleus of our cells. When a cell needs to make a protein, it makes an RNA copy of the recipe, in the form of mRNA. These mRNAs deliver the instructions to the cell’s protein-making machinery, until, after a few hours or days, they break down and protein production ceases.

A new recipe

Back in 1990, in experiments in mice, biologists demonstrated that it was possible to add either DNA or mRNA coding for a protein to living cells and get them to churn out that protein. What made this so exciting is that DNA and RNA are much easier to produce in the lab than proteins. It showed that, once you have the code you need for the mRNA to make a protein to prime the immune system for a given virus, you should be able to crank out a prototype vaccine remarkably quickly. “You are not relying on any biological processes during the manufacture, so it’s a much more straightforward process,” says Cullis.

But as often happens in biology, going from theory to practice was easier said than done. A big issue was that, because many viruses and parasites use forms of RNA to hijack cells, our bodies have lots of defences against it. Our blood, sweat and tears contain enzymes called RNAses that rapidly chew up any RNA found outside cells. And if foreign RNA does get inside cells, it triggers an array of defences. “Your body has evolved to have all these mechanisms to sense RNA viruses,” says Anna Blakney at the University of British Columbia.

Of course vaccines need to set off the immune system’s alarm bells, summoning cells that target any foreign material they find. But the response to RNAs introduced into the body is so strong that they are destroyed before the desired protein can be made. For these reasons, most biologists thought mRNA vaccines were a non-starter and focused on developing DNA-based vaccines instead. But that has yet to lead to much: so far, trials of DNA vaccines have been disappointing, failing to provoke a strong immune response.

Then in 2005, came the first of two critical developments that transformed the prospects for RNA versions. That year Katalin Karikó and Drew Weissman at the University of Pennsylvania managed to chemically...
modify mRNAs to dodge immune detection inside cells. With fewer added mRNAs being destroyed by cellular defences, protein production rose up to 1000-fold.

**Perfect packaging**

Secondly, other research groups had figured out ways of packaging RNAs in tiny oily balls called lipid nanoparticles that protect them from RNases in the blood and get them into cells. This approach had to overcome a big challenge. RNA is negatively charged, so will only combine with positively charged lipids, but positively charged lipids are toxic, says Cullis, who helped develop the lipid nanoparticles used to package the Pfizer/BioNTech vaccine. “They tend to rip cells apart.”

The clever solution was to develop lipids that are positively charged to begin with, allowing the RNA to be encapsulated, but lose this charge inside our bodies. This key technology has been gradually refined over many years. During the 2010s, human trials of a drug called patisiran, which uses another kind of RNA called small interfering RNA, or siRNA, showed that lipid nanoparticles are safe and paved the way for their use in mRNA vaccines.

Around the same time, the enormous promise of mRNA vaccines was starting to become clear. In March 2013, some 100 people in China became infected with H7N9 bird flu. When the genetic sequences of the virus were posted online, a team at pharmaceutical firm Novartis created a potential mRNA vaccine from scratch in just eight days.

Within weeks, the vaccine candidate was shown to produce a good response in mice. The work set an astounding new speed record – getting to this stage can take a year or more with conventional vaccines. But the outbreak ended and this work wasn’t taken further. Progress remained slow. Big pharma companies didn’t see much profit in pursuing a new and unproven vaccine technology, and left it to smaller companies such as BioNTech and Moderna. “Everybody was sceptical about it,” says Blakney.

When the pandemic began in 2020, there had been many small trials of mRNA vaccines, mostly designed to treat cancers by inducing

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**Injection of hope**

After the triumph of mRNA vaccines for covid-19, investment in this technology has skyrocketed. Already this year, 71 mRNA vaccine trials have been announced or begun, says Jessica McCormack at analytics firm GlobalData, compared with just two in 2018. The vast majority are for infectious diseases.

The hope is that mRNA vaccines can do three things: provide better alternatives to existing vaccines, such as the BCG vaccine for tuberculosis; accelerate the development of vaccines against diseases for which there are none, from HIV to herpes; and allow us to respond to future pandemics even faster.

When it comes to improving on existing vaccines, flu is high on the list, says Anna Blakney at the University of British Columbia in Canada. Seasonal flu vaccines are just 30 to 40 per cent effective. “It’s just dismal,” she says.

Most flu vaccines are still made by growing the virus in eggs before modifying it for use as a vaccine, a long process. This means that, for the northern hemisphere, the flu strains to be included in a jab have to be chosen around February. By the time flu season hits in October, the circulating strains have changed a lot, says Blakney. “That’s where RNA vaccines could make a big difference.”

Another advantage of mRNA is its flexibility, says Nor bert Pardi at the University of Pennsylvania. It should be possible to vaccinate against 10 or more diseases at once. Moderna, for instance, is working on a combined seasonal vaccine against a range of viruses, including respiratory syncytial virus (RSV), human metapneumovirus (hMPV), flu and SARS-CoV-2, which causes covid-19.

mRNA technology might also boost efforts to develop vaccines against several types of flu virus, including those in animals that could jump into people and cause a pandemic. “If you can develop a broadly protective or universal flu vaccine before the next pandemic, you don’t need to worry about time,” says Pardi.

There are also efforts to use the mRNA approach to develop a pan-coronavirus vaccine, better fend off malaria and finally create a vaccine against HIV. Both BioNTech and Moderna are working on HIV candidates, and Moderna started a clinical trial of one in August. “We have a good chance of coming up with an HIV vaccine,” says Pardi.

Still, caution is warranted. It is too early to know how much long-term protection mRNA vaccines provide. A UK study found that while the Pfizer/BioNTech vaccine provides higher protection against the delta coronavirus variant than the non-mRNA Oxford/AstraZeneca vaccine, its effectiveness also declines faster. Long-term effects of mRNA vaccines might also turn out to be different to those of other vaccine types, says the study leader Sarah Walker at the University of Oxford.

And while the mRNA covid-19 vaccines have proved safe, they can cause fatigue, headache and fever. There is some evidence that these effects are related to the quantity of RNA injected, says Blakney.

Self-amplifying mRNA vaccines, where the mRNAs delivered to cells include one that codes for enzymes that make more copies of the mRNA for the viral protein, could help resolve this. Because they contain less RNA, they might reduce adverse effects and be quicker to make.

Storage is also an issue. Existing mRNA vaccines have to be kept frozen. Cullis thinks it will be possible to keep future mRNA vaccines in a fridge, but doubts room temperature will ever be feasible.
Over many years. The deadly kidney disorder known as aHUS can be treated with an antibody called eculizumab, for example, but it is one of the world’s most expensive drugs, costing some £300,000 a year.

The big hope is that, if we can use mRNA to shift the medicine-making step into our bodies, we could produce the same therapies at a fraction of the cost – and produce new ones much faster.

The advantages become clear if we understand the difficulties of making proteins such as antibodies in a factory. The function of proteins depends on them folding into precise shapes, which can only happen correctly in living cells. This crucial shape then has to be carefully preserved during purification and storage, and all of these steps have to be tailored for each different protein. Not so with mRNAs, because it is just the information they encode – the sequence – that matters. They can be made chemically, without living cells, and the same production process can be used every time. “It’s a huge advantage,” says Blakney. “It cuts down on that bottleneck.”

Getting the body to make antibodies directly is a bit different to a vaccine. With a vaccine, only a tiny amount of viral protein is needed and its production has to be limited to one small part of the body because foreign proteins trigger inflammation – shoulder muscles are convenient and safe. For other applications, larger quantities of mRNAs are injected into the blood, where they are almost all taken up by liver cells that produce the specific desired protein and release it into the blood. Essentially, this turns the liver into a bioreactor for producing almost any protein-based drug.

It was only in 2017 that Norbert Pardi at the University of Pennsylvania showed in mice that this was possible, so these kinds of mRNA therapeutics are still at an early stage. Moderna is leading the way. In 2019, the company reported positive results from the first tests in people of an mRNA directly coding for an antibody against chikungunya virus. And it isn’t just antibodies, but any proteins: in August this year, Moderna started trials for an mRNA coding for a signalling protein designed to treat autoimmune disorders and another that treats an inherited disease by triggering their destruction by the immune system, they can also be designed to help tamp down an overactive immune response as happens in auto-immune disorders.

Antibody-based drugs are already being used to treat these conditions, a range of infectious diseases and even migraines. They can be extremely effective, but the downside is that they are difficult and time-consuming to produce and incredibly costly as a result. These costs can add up to huge sums with conditions that require regular injections of antibodies over many years. The deadly kidney disorder known as aHUS can be treated with an antibody called eculizumab, for example, but it is one of the world’s most expensive drugs, costing some £300,000 a year.

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replacing a faulty enzyme. If these kinds of trials are successful, we could see an explosion of mRNA-based treatments. That would bring many advantages, not least that far fewer injections or infusions of protein therapies should be required. A single dose of mRNA can drive protein production for days, and it is also possible to chemically tweak mRNAs so they persist for longer than that.

**Possible lags as therapeutic proteins ramp up to speed**

Possible lags as therapeutic proteins ramp up to necessary levels for treatment may not actually be so significant either. With mRNAs, there will be a slight delay compared with injecting antibodies directly, but it is so minimal it doesn’t seem to matter, even for conditions that require urgent treatment such as poisoning. A recent study in mice, for instance, found that injecting mRNA was just as effective at protecting against lethal doses of botulinum toxin as injecting antibodies directly.

The potential uses of mRNAs will be even greater if we can find ways of delivering them to specific organs or tissues such as the brain or bone marrow. Many genetic disorders are caused by the lack of functional proteins within certain tissues. So far though, getting mRNAs anywhere besides the liver is proving very difficult to do other than by direct injection, says Cullis. But that approach may be good enough for some purposes. Human trials are already under way of Moderna’s AZD8601, an mRNA treatment designed to spur blood vessel growth in wounds that won’t heal or in tissue damaged by heart attacks, for instance.

Where successful treatment requires getting mRNAs into a higher proportion of cells in a specific tissue or organ than can be achieved by direct injection, there is still some distance to go. One strategy is to put mRNAs inside the empty shells of viruses known to target specific cell types, and so deliver the genetic material into a desired tissue that way. The trouble is that the immune system starts attacking the viral shell, so this method cannot be used repeatedly. In August though, one team reported that it had managed to make viral shells from a human protein, potentially solving this problem. “I think it’s definitely doable,” says Blakney. “But there’s a lot more work that needs to be done.”

Then there’s the use of mRNA against cancer. The general idea of cancer vaccines is to get a person’s immune system to target proteins found on tumour cells, but not healthy cells. Many cancer vaccines are personalised: an individual’s cancer is genetically sequenced to identify targets, typically mutant proteins that have arisen in their tumour cells.

The big advantage of the mRNA approach is that cancer vaccines can be produced quickly and relatively cheaply as soon as such targets are identified. But finding targets specific to tumours is difficult, says Smita Nair at Duke University in North Carolina. Nor is it easy to get the body to attack the tumour proteins, because they are similar to those in normal tissue, which are usually off limits to the immune system. “Cancer is much more difficult [than infectious diseases],” she says. “It’s a work in progress, but looking hopeful.”

There are currently six ongoing phase II trials of mRNA vaccines for cancer that could potentially lead to approvals, says Jessica McCormack, an analyst with GlobalData. Four of these are personalised vaccines.

While there is no doubt that mRNA vaccines and therapeutics hold enormous promise (see “Injection of hope”, page 40), there are reasons for caution. The chikungunya antibody trial remains the only such test of therapeutic protein production in the body so far and the full results haven’t yet been published, says Pardi, so we can’t yet say for sure that this approach is both safe and effective in people. “Toxicity testing will be absolutely essential,” he says.

But all the indications from trials in animals, including non-human primates, are positive, and the potential is staggering. If we can overcome the remaining challenges – and that’s a big if – we could wield the very tactic that viruses use against us to treat almost any condition that ails us.

In one sense, there isn’t actually a lot that is revolutionary about mRNA vaccines and therapeutics. An mRNA vaccine is a way of getting a viral protein inside the body, as is a subunit vaccine. An mRNA antibody therapy is just a way of delivering an antibody into someone’s bloodstream, as is injecting it directly. The end product – the protein – is the same.

But in terms of how fast you can develop and test treatments, and get them to large numbers of people, mRNA technology is utterly transformative. Less than a year after they were first rolled out, mRNA vaccines have already saved hundreds of thousands of lives. “These medicines are just incredible,” says Cullis.

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**Covid vaccines: mRNA recipes are delivered to our cells encased in an oily package**

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