mRNA vaccines: hope beneath the hype

mRNA vaccines have proven themselves as the most effective covid-19 vaccines, and their makers are now seeking to help conditions from cancer to HIV. Andy Extance investigates their promise and limitations

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The next decade will “see a revolution in mRNA therapeutics,” says Paul Burton, chief medical officer at Moderna in the United States. Along with Germany based BioNTech, Moderna has already shown, by changing the course of the covid-19 pandemic, how powerful medicines based on messenger ribonucleic acid (mRNA) can be (box 1). The companies had originally planned to use their technology for other conditions, particularly cancer. After more than 10 years spent developing the technology, they’re now set to use their covid-19 success as a springboard to achieve their original goals.

Box 1: How mRNA covid-19 vaccines work

Until 2020, most vaccines used either disabled forms of bacteria or viruses or protein molecules that form part of the shell that wraps around the genetic material at their centre. Covid-19 vaccines from Moderna and BioNTech instead deliver a genetic molecule called messenger RNA (mRNA) directly to cells. These encode an antigen—namely the spike protein from the outer coating of SARS-CoV-2 that lets the virus grab onto our cells. The human cell’s own machinery then makes the antigen from the mRNA template and the resulting protein provokes an adaptive immune response. Thus, the body learns to identify, target, and destroy that protein, including live virus particles.

As Moderna’s Paul Burton puts it, they “use your body’s cellular machinery to translate that messenger RNA into a protein that is perfectly designed for human beings.” Dealing directly with the genetic sequence makes vaccines much faster to develop than traditional methods.

Box 2: Vital mRNA innovations

Foreign mRNA would usually be detected and destroyed by the body’s immune system before it could be turned into protein. In 2005, University of Pennsylvania researchers Drew Weissman and Katalin Karikó swapped one of the four bases comprising the letters of the RNA genetic code, uridine, for an alternative, called pseudouridine. The mRNA made using pseudouridine was able to evade the immune system’s detection, paving the way for mRNA treatments. mRNA is also naturally broken down in cells. To maintain its viability for longer while it does its job, the mRNA is encased in fatty lipid molecules, forming tiny nanoparticle balls. “It’s a platform technology that we can reproducibly use,” Moderna’s Paul Burton told The BMJ. “The fidelity is extremely high.”

The pandemic “allowed the technology to come of age,” says Robin Shattock, professor of mucosal infection and immunity at Imperial College London. “It’s had quite a long and chequered approach to getting to something that works. But, now it’s there, that will cause a huge amount of investment and further technological advances.”

“Immunologically, mRNA enables very, very good vaccines,” says Akiko Iwasaki, professor of immunobiology, epidemiology, and molecular, cellular, and developmental biology at Yale University. “When the phase III [covid-19 mRNA vaccine] trial data were coming out, I was very excited about the incredible efficacy.” Both BioNTech and Moderna’s vaccines have attained efficacy levels above 90% in preventing covid-19. That ranks close to the most successful existing vaccines, such as those for hepatitis A, for which efficacy nears 100%.

Covid-19 was a better proving ground for mRNA vaccines than other conditions, says Paul Hunter, professor in medicine at the University of East Anglia. “Coronaviruses were always going to be an easy target for a vaccine,” he says. That’s because the SARS-CoV-2 virus’s spike protein is an obvious target for antibodies to block.

The relative ease of developing mRNA vaccines may improve prospects for diseases for which it is currently not economically viable to develop vaccines. Hunter concedes that mRNA vaccines still face the very large costs of testing vaccines in clinical
trials, and he warned that not all viruses are as easy to target as SARS-CoV-2.

**Becoming first choice**

The speed with which companies can develop mRNA vaccines means that this technology will also be “a first choice platform to test other pathogens,” says Iwasaki. It took Moderna seven weeks to produce its covid-19 vaccine and send it off for testing. By contrast, it can be at least three months before flu vaccines made using traditional approaches can be tested. That speed, however, combined with mRNA vaccines’ novelty, has contributed to some people’s hesitancy about receiving them. “That’s a major hurdle,” Iwasaki told *The BMJ*, although she believes that those with conditions like cancer might be less hesitant if mRNA therapy proves to be effective, particularly when treatment options are limited.

Personalised cancer vaccines will be an especially important area for driving investment, Shattock says. This is the area that both Moderna and BioNTech were founded to investigate. The approach here involves identifying proteins specific to a patient’s tumour and then making a vaccine specifically targeting them. Burton says that Moderna’s cancer vaccines, currently in phase II clinical trials, can contain more than 30 different mRNA sequences for different personalised antigens. The company’s technology is now advanced enough that this is no more challenging than the single sequence covid-19 vaccine, he added.

Vaccines with multiple mRNA sequences could help other conditions, like cytomegalovirus, which can cause birth defects and organ transplant complications. Cytomegalovirus’s outer coat comprises six proteins. “That’s very difficult to generate a vaccine against using standard technology,” Burton emphasised. Cytomegalovirus is the therapeutic area in which Moderna is furthest advanced after covid-19, having started phase III clinical trials in October 2021. Without the accelerated development timelines regulators brought in for the pandemic, phase III trials for vaccines typically take two to four years to complete.

The mRNA vaccine platform offers high fidelity that could also benefit flu vaccines, where traditional inactivated virus vaccines often suffer from mutations that make them less effective. In addition, vaccine production could start later, because mRNA vaccines can be manufactured more rapidly, enabling more informed decisions about what strains to include.

These two advantages might improve the 40-60% protection against infection that existing flu vaccines offer. But to bring mRNA flu vaccines to market they must match or beat the protection offered by existing vaccines at an affordable price. That is a different challenge to the one that faced manufacturers developing vaccines against covid-19, where there were no existing treatments.

Moderna started conducting phase I trials for a flu mRNA vaccine in 2015, using two strains (H10N8 and H7No) for which there were no other vaccines. The Moderna vaccines generated immune responses, validating the mRNA approach, but immunity was short lived. In July 2021, it launched a 180 person phase I/II trial of a flu vaccine containing four mRNA sequences targeting four different strains, expected to run through early 2022.

Based on usual vaccine development timelines, a commercial mRNA based flu vaccine is likely to be on the market in four to seven years. Moderna’s is the leading candidate, but BioNTech’s covid-19 vaccine partner Pfizer is developing a flu vaccine independently under the two companies’ collaboration agreement, which is now in phase I testing. Sanofi is also developing an mRNA based flu vaccine, and GSK is partnering with CureVac on both flu and second generation covid-19 mRNA vaccines.

Meanwhile, Moderna has vaccines for chikungunya, Epstein-Barr virus, metapneumovirus, Zika, and respiratory syncytial virus in development. The company is also exploring delivering multiple mRNA sequences to vaccinate against several viruses at once. And it is also working on what would be the world’s first HIV vaccine, which the company is preparing for testing in humans.

Iwasaki emphasises the size of the challenge here. HIV mutates rapidly, changing its proteins’ shapes and making it difficult to target. Even mRNA might be unable to overcome that. Existing mRNA technology might also be unable to protect against the herpes virus, which has also never had a working vaccine. “For those types of pathogens, we may need additional tweaks to make the vaccines more effective,” Iwasaki told *The BMJ*. She notes, for example, the need for vaccines to generate “the right type of immunity in the right type of tissue.” For SARS-CoV-2, mRNA vaccines stimulate the immune system to produce circulating memory T cells and B cells. Herpes vaccination could benefit from resident memory T cells forming in genital mucosal tissues. “This kind of localised mucosal immunity can be developed, but not with the current technology,” Iwasaki says.

**Equity**

Even if mRNA vaccines can treat some of the conditions with the greatest unmet need, many of these diseases are most common in developing countries. To reach those regions, companies like BioNTech and Moderna will have to share manufacturing know-how with local factories, Iwasaki says.

With the pandemic ongoing, and booster jabs now in the conversation, covid-19 looks to be the workhorse of the mRNA vaccine industry for the near future. To make its covid-19 vaccine more widely available, Moderna works with organisations like the World Health Organization backed Covax initiative. Moderna has also lowered the vaccine dose in its boosting shots, which, says Burton, “will free up maybe a billion doses in 2022 that can be deployed around the world.”

Asked whether the cost of mRNA vaccines is a barrier to access in developing countries, Burton says that mRNA covid-19 vaccines had provided good value. But Moderna has so far declined to share its technology blueprint to allow companies in other countries to make the vaccine domestically, instead reportedly planning a $500m manufacturing facility of its own in Africa. Meanwhile, WHO and its Covax partners are working with a South African consortium to establish a covid-19 mRNA vaccine technology transfer hub. And in October 2021, BioNTech signed an agreement with the Rwandan government and Institut Pasteur de Dakar in Senegal to build an mRNA production facility starting in mid-2022. A major challenge to expanding manufacturing capability is that mRNA vaccines must be kept very cold to remain stable. And even though storage temperatures for covid-19 vaccines have increased from −70°C to −20°C, availability of suitable freezers remains a barrier, Iwasaki says.

Stability is a particular problem for covid-19 vaccines because they have long mRNA sequences to encode the spike protein, which contains 1273 amino acid building blocks. Burton told *The BMJ* that this will be less of a problem in other conditions, allowing storage at higher temperatures. “If you can shorten that, it stabilises the whole particle,” he says. Burton added that Moderna is developing
its lipid nanoparticle technology to increase storage temperatures even further.

Robin Shattock thinks that mRNA medicines will ultimately become more available because the capacity to make them will increase in different parts of the world. Experts say that the technology is easier to establish from scratch than traditional vaccine manufacturing, which requires large vats of cell culture that can be subject to variations in yield and vulnerable to various hiccups.²⁸

Traditional vaccines need a big factory to make the protein or the virus, which takes a long time. One bottleneck is making modifications like adding glucose residues, says Burton, which our bodies do much faster. “The amazing thing about mRNA is it goes into the cell, uses your body’s cellular machinery to translate into a protein, and then it’s naturally modified. The ability to make complex antigens in large amounts, it opens up so many diseases.”

Competing interests: I have read and understood BMJ policy on declaration of interests and have no relevant interests to declare.

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