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On January 10, 2020, the genome sequence of what was then the ‘novel coronavirus’ was published. Soon after, researchers around the globe started using the information to develop novel vaccines. The sequence revealed that the RNA genome of the virus now known as SARS-CoV-2 only encodes four proteins, namely the spike, envelope, membrane and nucleocapsid proteins. As the spike proteins protruding from the spherical shell of the virus like antennae are both the first contact point with human cells and a crucial tool for docking onto the cell’s angiotensin-converting enzyme ACE2, all vaccine development efforts, if they weren’t using the entire virus, focused on creating an immune response against the spike protein or parts of it.

As the events unfolded and the pandemic ran out of control in many countries, this work became an urgent priority. Astonishingly, developmental steps normally taking years were completed within months. Moreover, the conditions of a new disease spreading rapidly facilitated the enrolment of participants for clinical studies. By definition, the majority of the population was naïve to the new pathogen, and for the phase III trials, where protection is determined, there was no shortage of people naturally becoming exposed to it after receiving the vaccine or the control treatment. This explains why, in spite of the very rapid development, the trial results are as robust as for any other new vaccine getting approved.

Within a year of the sequence report, eight vaccines were approved by at least one country. These fall into three separate categories, including one that didn’t exist in the market a year earlier.

The classic
Classical vaccinations, starting with variolation and the use of cowpox to immunise against the pox, rely on weaker variants or attenuated versions of the pathogen they target. While they are conceptually simple, they come with the risk that the variant could become more virulent or cause an overreaction of the immune system.

This should be ruled out in the approach using inactivated rather than attenuated viruses, ensuring that the virus particles, while physically intact, cannot replicate in the patient under any circumstances. Vaccination against rabies, for instance, has undergone this progression, from the attenuated virus used by Pasteur in 1885 to inactivated virus particles. Typically, this involves viruses being replicated in Vero cell cultures (a cell line derived from the kidney epithelial cells of monkeys) and then treated with a chemical, such as formaldehyde. Production of the viruses requires a biosafety level 3 facility, and this is a disadvantage in comparison with purely synthetic vaccines.

Several vaccines developed in China are based on chemically inactivated versions of the coronavirus. The company Sinovac uses it in combination with aluminium hydroxide as an adjuvant in its vaccine CoronaVac, which has been approved for emergency use in China, as well as in Indonesia, Brazil and Turkey.

Another Chinese company, Sinopharm, has pursued separate developmental projects with research labs in Wuhan and Beijing. The Wuhan vaccine, BBIBP-CorV, has won regular approval in China, Bahrain and the United Arab Emirates, as well as emergency approval in several other countries.

The Indian Council of Medical Research together with the company Bharat Biotech in Hyderabad, India, are also following this approach for their vaccine, BBV152 (Covaxin). India approved emergency use of this vaccine at the beginning of January, even though results of the phase III clinical trial begun in late November had not been reported yet.

Viral vector vaccines
A second long-established path to new vaccines is the use of a

Way out: With the coronavirus spreading out of control in many countries around the world, mass vaccinations have become essential for ending the pandemic. (Photo: Baltimore County Government.)
non-replicating virus as a carrier for elements of the target disease required to raise the immune response. This method is referred to as the vector approach. The vaccine group at the University of Oxford, UK, has spent the last decade developing and applying such a vector, based on an adenovirus that causes the common cold in chimpanzees. Although the group has also used human adenoviruses, they switched to the chimpanzee version to avoid patients’ pre-existing immunity to the vector.

The Oxford researchers have used this platform, called ChAdOx1, for the development of candidate vaccines against various diseases, including one against Middle East Respiratory Syndrome (MERS), which belongs to the same family as SARS-CoV-2. The MERS coronavirus (MERS-CoV) is more lethal but less infectious than SARS-CoV-2. Therefore, its outbreaks after repeated zoonotic transfers from camels have mostly remained limited to the Middle East (Curr. Biol. (2020) 30, R191–R194), but having a vaccine may save lives in future outbreaks. The Oxford MERS vaccine has undergone phase I clinical trials in the UK. Further trials in Saudi Arabia were interrupted by the pandemic.

As part of the WHO programme of preparedness for an epidemic for an as yet unidentified Disease X, the Oxford lab was ready to use the ChAdOx1 platform for new challenges. Thus, as soon as the sequence information was available and COVID-19 started to spread around the globe, the researchers, led by Sarah Gilbert, set off to use their platform and their experience to fight this new disease.

After successful animal trials, they started recruiting participants for clinical trials at the end of March. For the scale-up of trials and production, they entered a collaboration with the pharma company AstraZeneca. Although the clinical trials moved much faster than they usually do in vaccine development, scientists from the vaccine group emphasise that they tested as much and as thoroughly as with any other vaccine. More than 30,000 participants were involved in the trials by the end of 2020, at which point preliminary phase III results were reported and the UK approved the vaccine for emergency use. By January 13, it gained similar approval in India, Morocco, Argentina and El Salvador.

The same principle was also used in the Russian ‘Sputnik V’ vaccine, which is already being used in Russia, as well as in the one from the Chinese company CanSino Biologics, which has gained approval for emergency use in China.

RNA messages

The surprise winner in the race to get a COVID vaccine approved under the strict rules of the relevant EU and US authorities, however, came from a completely new direction. The biotech start-up BioNTech at Mainz, Germany, was co-founded and is still led by the married couple Ugur Sahin and Ozlem Tureci, who wanted to use messenger RNA to engineer the immune system for a variety of medical purposes, including personalised immunotherapy of cancer as well as treatment of autoimmune disease. The first successes that put their start-up on the map date only a few years back. They have recently published preclinical results of a potential treatment for multiple sclerosis (Science (2021) 371, 145–153).

When COVID-19 emerged, they had the idea to use their established mRNA delivery platform for a vaccine. The coronavirus essentially uses mRNA as its genome, so the approach, while a novelty for vaccines, wouldn’t stray that far away from the way the virus works. Instead of a virus particle, the BioNTech approach involves packaging the mRNA in lipid nanoparticles (LNPs).

Researchers at BioNTech first tested two different mRNA constructs, one coding for a trimer of the receptor-binding domain of the spike protein and the other for the entire spike protein with two proline residues engineered in for extra structural stability. Initial trials showed that this second version produced less-significant side effects than the first, so the one with the engineered full-length spike protein, BNT162b2, went forward into full-scale clinical trials conducted in collaboration with the US pharma company Pfizer.

Phase III trials with more than 40,000 patients showed that, one week after the second dose, more than 90% were protected from becoming seriously ill with COVID-19. To what extent the vaccine also blocks mild forms and transmission of the disease remains to be established. Moreover, the test results obtained by December 2020 were insufficient to back its use for pregnant women and children under the age of 16.

On December 2, fewer than 11 months since publication of the
coronavirus sequence, the vaccine, now known as Tozinameran (Pfizer’s trade name is Comirnaty), was approved for emergency use in the UK. On December 21, it obtained full regulatory approval by the European Commission. Approval in the USA by the FDA and in many other countries followed.

Apart from the sheer volume of production needed to protect the world from a pandemic, the main challenge connected with Tozinameran is the logistics of vaccination. As it requires storage at –70°C, it is difficult to distribute in remote areas where deep-freeze facilities may not be available.

The US company Moderna (whose name hints at the philosophy of using modified RNA) at Cambridge, Massachusetts, working with the National Institute of Allergy and Infectious Diseases (NIAID), has used a similar approach, also packaging a messenger RNA for an engineered version of the spike protein in LNPs. In addition, the Moderna formulation contains stabilisers including ethylene glycol, which presumably accounts for the easier storage. This vaccine, called mRNA-1273, keeps for a month in an ordinary refrigerator, or four months at –20°C. It has obtained authorisation for emergency use in the USA, UK and Canada, and full regulatory approval in the EU.

Other options

As of mid-January there are eight vaccines that have been approved for either regular or emergency use by national authorities. All of them fall into one of the categories discussed above. However, in the queue of vaccine candidates still being tested, there are also other approaches represented.

Thus, the US company Novavax aims to apply the spike protein in the shape of protein nanoparticles, using an approach also known as a subunit vaccine. A phase III clinical trial of their candidate vaccine is currently under way in the USA and Mexico. Several other companies are also working with protein constructs based either on the entire spike protein or on its receptor-binding domain. The Finlay Institute in Havana, Cuba, has launched a phase II trial for a candidate vaccine hitching the spike protein to the tetanus vaccine, which consists of an inactive version of the tetanus toxin protein, known as the tetanus toxoid.

The Canadian company Medicago is using virus-like particles (VLPs) due to be expressed in engineered Nicotiana plants. Phase II trials of their candidate vaccine started in November.

Overall, the pandemic has given vaccine development a unique boost, producing both faster results and new approaches. Developmental steps that normally take years were accomplished within months.

As the control of the epidemic has failed in multiple countries, including the USA, UK and Brazil, vaccines are now widely seen as the only way that the world can emerge from the COVID crisis. Public trust in the vaccines is crucial to ensure the required level of participation, as Anthony Fauci from the NIAID and colleagues have highlighted in a review of the situation in the USA (Ann. Intern. Med. (2021) https://doi.org/10.7326/M21-0111).

The question of whether the virus can evolve to overcome the protective effect of the existing vaccines has come to the fore. SARS-CoV-2 mutates relatively rarely compared with other RNA viruses (Curr. Biol. (2020) 30, R1455–R1457), but, due to the uncontrolled spread of the virus in many areas providing ample replication cycles for it, there are now several new variants that cause concern as they may be more infectious than the original strain discovered in Wuhan.

So far, none of the mutations identified appear to be able to sidestep the existing vaccines. Should a vaccine-evading variant evolve, however, some of the vaccines, including the novel mRNA vaccines, could be adapted to a new virus sequence within weeks. The same promise holds if another new coronavirus crosses species barriers to spread among humans, and this could happen at any time. With the lessons of the first COVID year, we will be better prepared the next time.

Q & A

Peter Sterling

Peter Sterling is currently Professor of Neuroscience at the University of Pennsylvania. He arrived in 1969 and closed his laboratory in 2009. By then he had moved to a small farm in the mountains of western Panama, from whence he explores tropical agriculture and life among indigenous peoples in Central America while continuing to write. His books include Principles of Neural Design with Simon Laughlin (2015) and What Is Health? (2020), which draws on neuroscience, plus his lifetime of social activism.

What drew you to biology? I grew up in the woods and salt marshes near a small town 30 miles north of New York City where I’d collect live amphibians and reptiles, insects, nests, and so on. My bedroom was a zoo/museum. I haunted the American Museum of Natural History in New York City, and now when I am hiking and encounter a misty bog with lichens dripping from snags it feels like a museum ‘diorama’ — but sadly never as vivid.

I was drawn to neurobiology by Howard Schneideman, my first mentor at Cornell University, who opened many lectures by reading Sir Charles Sherrington’s neuro-poetry — the brain as “an enchanted loom where millions of flashing shuttles weave a dissolving pattern, always a meaningful pattern though never an abiding one”. When the poetry was followed by an opportunity to stimulate a nerve and record the muscle contractions on a revolving smoked drum, I never looked back.

Might you have had an alternative career? During my second year, Black students across the US South were ‘sitting in’ at lunch counters for the right to use public facilities. I organized Cornell students — all white — to picket the local Woolworths, whose southern stores were segregated. Next winter (1961), Patrice Lumumba was murdered in the Congo under CIA sponsorship, and this was followed that spring by the CIA-sponsored counter-revolutionary invasion of Cuba at the Bay of Pigs. I participated in campus