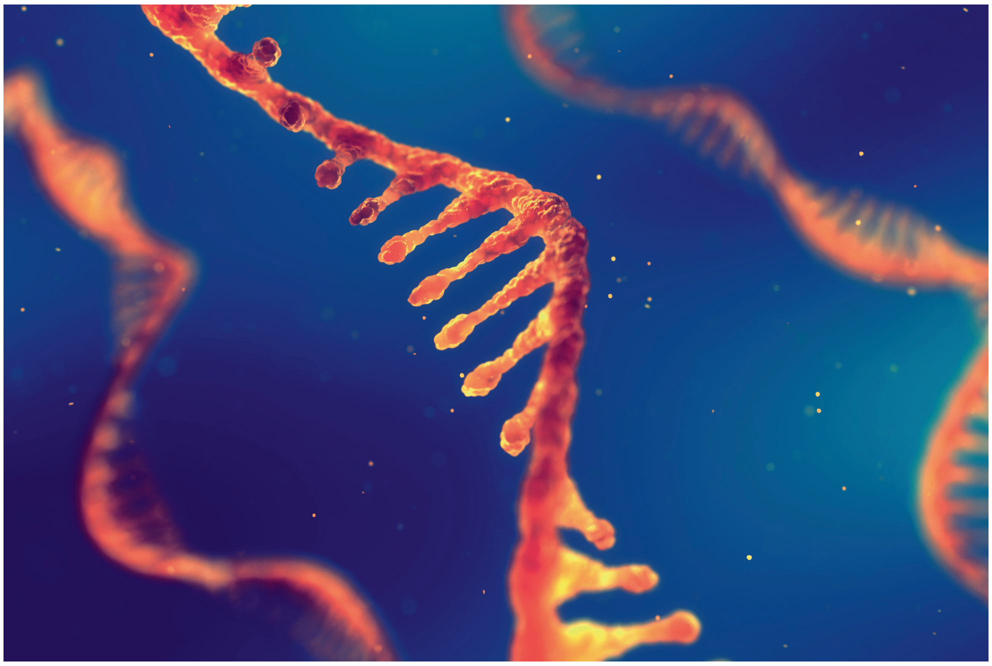
HOW TO BUILD AN MRNA ARSENAL FOR PANDEMIC PREVENTION

Through in-house research, academic collaborations and global team building, **MODERNA CREATES AN ECOSYSTEM** for innovation and manufacturing.

The current COVID-19 pandemic has claimed an estimated 18.2 million lives globally[1], but it could have been worse. Without vaccines, the death toll could have been closer to 40 million[2]. A future pandemic, set off by a putative 'Disease X', could be even worse, and health-care experts want to be prepared.

Disease X, in this instance, is the unknown pathogen, as designated by the World Health Organization (WHO), with potential to cause a serious international epidemic. And it's probably not far away. One study[3] estimated up to a 2% chance per year of another pandemic at least as bad as COVID-19, which means a one in five chance over the next ten years. That's why scientists at Moderna are planning for Disease X today.



▲ Messenger RNA technology makes it easier to translate information into a vaccine and do it faster.

The company's plan views global health in a broad way. "It's about looking at overall disease burden," says Shannon Klinger, chief legal officer at Moderna, and president of the Moderna Foundation in Cambridge, Massachusetts. "We see that people living in low-income countries are far more likely to die of a communicable disease than a non-communicable disease."

The technology behind Moderna's COVID-19 vaccine — mRNA packaged in lipid nanoparticles — has the potential to reduce disparities in global health and help fight future pandemics. "We think that our mRNA platform is uniquely situated to address some of these challenges, challenges that our industry has been trying to fight for decades," Klinger says. "Part of our global public health strategy is aimed at advancing our mRNA vaccines for the prevention of infectious diseases and investing in the next generation of mRNA innovation."

Moderna's current pipeline includes numerous programmes relevant to public health, including new vaccines for respiratory threats like COVID variants, influenza and respiratory syncytial virus. In early 2022, the company announced a portfolio of programmes aimed at tackling emerging pathogens, in preparation for Disease X threats. The company selected 15 diseases based on global burden and declaration of priority pathogens from the WHO and the Coalition for Epidemic Preparedness Innovations (CEPI). "They have issued calls to action to develop vaccines against particular pathogens," Klinger says. "Our portfolio already included four of those: SARS-CoV-2, HIV, Nipah and Zika." Now, Moderna will deploy its mRNA technology to research vaccine approaches for the remaining 11 pathogens, and one of its first objectives is to gather as much data as it can.

Prototypes against pathogens

Given the uncertainty of what Disease X could be, Moderna speeds up the development of new vaccines based on prototype pathogens. "We take examples from different viral families," says Andrea Carfi, Moderna's chief scientific officer, infectious disease. "This gives us a starting point to develop a new vaccine against a related pathogen." That starting point includes knowledge about viral structure, cell entry and the parts of the virus that might be the best targets for a vaccine.

Not only does a prototype pathogen suggest potential antigens to target, it also helps Moderna's scientists and their collaborators develop assays and models for testing a new vaccine's impact. "Testing is really fundamental to the development of a vaccine," Carfi says.

For COVID-19, Moderna used its knowledge from work on other coronaviruses to speed up development of its vaccine. Other tools also accelerate the creation of more vaccines. As an example, Carfi says, "The advances in applying structural biology to antigen design — really understanding the atomic details of these proteins and how to stabilize them — helps us engineer better vaccines." Plus, he points out that mRNA technology makes it easier to translate that antigen information into a vaccine and do it faster. "With mRNA approaches, you don't have to grow the virus to make a vaccine," he says. "Instead, you can use available sequence information and draw similarities to other viruses."

Many of the advances in structural biology arise from computation. "Ten years ago, we didn't think it would be possible to use artificial intelligence (AI), but it provides a very good starting point in terms of understanding the structure of viral proteins, especially on the surface of viruses," Carfi says. "It's a little tricky because those are very unstable products." He adds that expanding the database of structures will improve the AI-based training that allows algorithms to explore new viruses.

Together, these analytical tools transform the development of vaccines. "There's no old vaccinology; we combine structural biology, virology, immunology — bringing together all the different aspects of science," Carfi says. "There is no vaccine without understanding how the virus enters cells as infection develops and how to neutralize it."

▲ Vaccines that use mRNA technology have the potential to reduce disparities in global health and help fight future pandemics.

A case in point is Moderna's work on a vaccine against Nipah virus. Nipah is a zoonotic disease, which the WHO estimates has a fatality rate as high as 75%. "From other paramyxoviruses, where we know the structure of the antigens and how to stabilize them, we can apply that directly to Nipah," he says. "This work suggests the best antigen to target, but then we need to demonstrate that targeting the antigen provides protection," which requires the development of assays and animal models.

For global health, the best prototype pathogen to pick depends on which infections pose the highest risk. "It takes surveillance," Carfi says. "You need to really understand epidemiology and where there are outbreaks of infection." From those outbreaks, Moderna picks a prototype pathogen that is likely to provide the most information about a new infection.

Creating complex vaccines

To battle some diseases, a vaccine must take on a target composed of a multiprotein complex or several pathogens at once. "That's been very difficult with previous technologies," says Melissa Moore, Moderna's chief scientific officer, scientific affairs.

Latent viruses often express many antigens that trigger the production of antibodies. A key antigen for cytomegalovirus, for example, consists of a complex made of five subunits. Targeting that antigen requires a vaccine that recognizes all five subunits. "That really wasn't able to be made using standard biologics — making the proteins in cell culture and then trying to administer them," Moore says. Moderna is investigating a potential vaccine that can put the five needed mRNAs in one lipid nanoparticle to make a vaccine that targets all subunits.

Other combinations can also be created in mRNA vaccines. For example, a multi-valent vaccine can attack multiple strains of the same disease or even different diseases. Moderna's most recent COVID vaccine, authorized or approved by the United States Food and Drug Administration, European Medicines Agency and others, includes mRNA encoding the original strain of the virus plus several variants, including Omicron. In addition, Moore says that Moderna is "working on mixing together mRNAs targeting important respiratory viruses in order to make a combination vaccine". Although other examples of combination vaccines exist, such as the one for measles, mumps and rubella (MMR), making them with mRNA simplifies the manufacturing process — instead of growing multiple cultures of cells, just make the mRNAs and put them together.

Building community science

Beyond its in-house expertise, Moderna collaborates with the broader research community. Today's vaccines based on mRNA arose from years of research in academia and industry. "We could not have developed our mRNA vaccines without the decades of curiosity-based research into

▲ mRNA vaccinology combines structural biology, virology, immunology — bringing together all the different aspects of science.

▲ Moderna collaborates with scientists across academia and industry to advance medicines for Disease X.

understanding the molecular biology of mRNA," Moore says. "It was a cast of hundreds of thousands of people who enabled us to be able to do this."

For tomorrow's mRNA-based vaccines, Moderna has developed a programme that encourages collaborations between academic and industrial scientists. "Internally, we cannot generate all of the preclinical data for investigating all of the possible vaccines," says Moore. So, the company developed its mRNA Access programme, which provides tools for researchers to design novel vaccines for emerging and neglected infectious diseases.

Participating researchers can use Moderna's mRNA Design Studio. With this cloud-based tool, researchers can create mRNAs that might target emerging diseases or existing diseases in new ways. "This allows academic investigators to figure out new antigen designs, and we provide them with the formulated mRNA that targets that antigen," Moore says. "This is amazing technology, and we saw an opportunity to share it with researchers exploring vaccine-preventable diseases."

In fact, defeating future outbreaks of infectious diseases will require spreading vaccine manufacturing around the world. "What these outbreaks tell us is that, even when there is an approved vaccine, it's not always available in sufficient quantities to meet demand and be accessible to the populations most at risk," Klinger says. "That's why one of the things we announced as part of our public health strategy was manufacturing in Kenya." Compared with traditional vaccines, mRNA-based vaccines can be made in smaller facilities that cost less than traditional vaccine facilities[4], which makes it easier to build plants where the vaccines are needed. She adds that the Kenyan plant is expected to produce up to 500 million doses of vaccines a year.

During the COVID-19 pandemic, people around the world learned the value of collaboration. "We understand that pandemic preparedness requires public and private collaboration," Klinger says. "So while our platform enables us to move quickly, we must work with governments, health-care practitioners and other stakeholders to meet the challenges of future pathogens." And when it comes to tackling Disease X, Klinger says, "We are building an ecosystem to be better prepared moving forward."

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