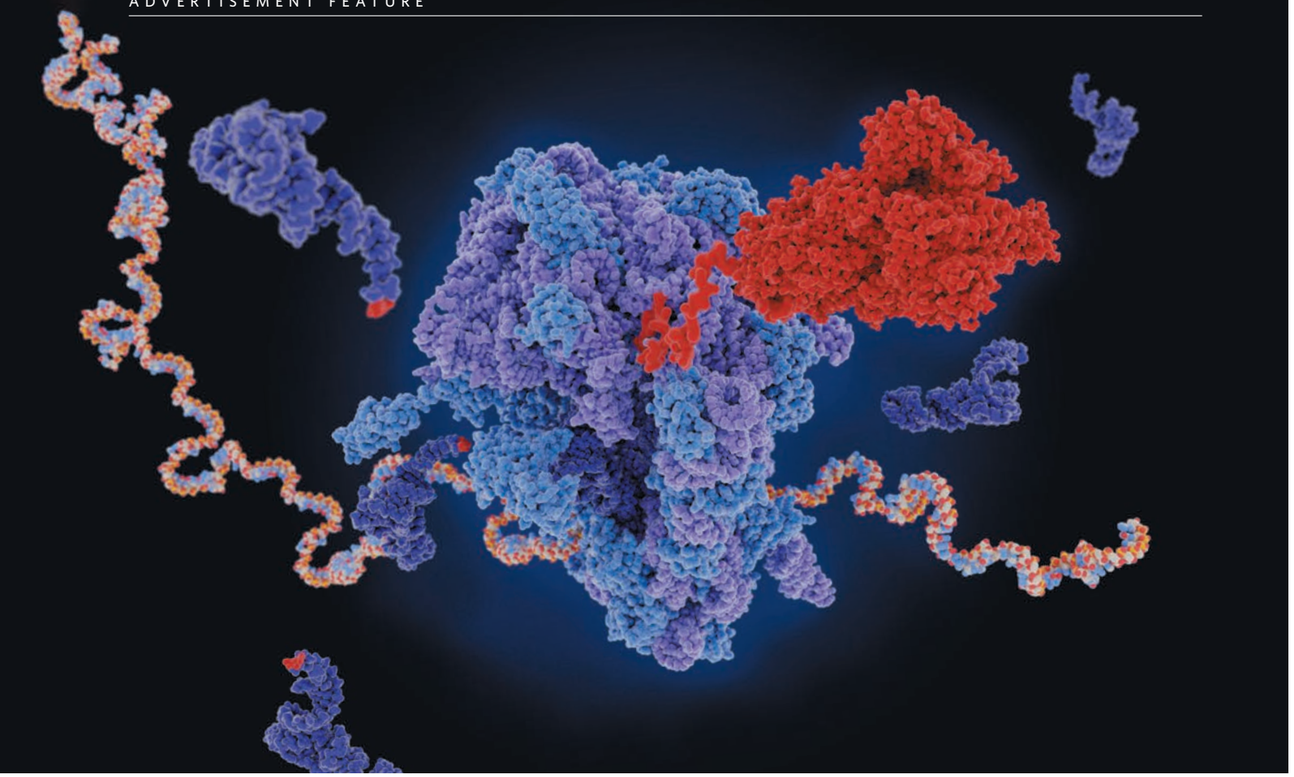

MRNA VACCINES AND TREATMENTS: BEYOND COVID-19

KNOWLEDGE TAKEN FROM MRNA TECHNOLOGIES used against COVID-19 is supporting development of vaccines and therapeutics to fight existing diseases and potentially thwart future pandemics.

The COVID-19 pandemic has triggered an unprecedented mobilization of resources to find vaccines and therapeutics to treat and prevent infection with SARS-CoV-2. mRNA technology was quickly adopted in the COVID-19 vaccine race and has undoubtedly proven its worth.

Less than a year after the emergence of COVID-19, an entirely new type of vaccine based on mRNA technology was authorized for emergency use. Many billions of doses of the Moderna and Pfizer/BioNTech mRNA vaccines have now been administered globally, saving millions of lives.

During the pandemic, there have been many learnings and breakthroughs, which will improve preparedness and responsiveness to future disease outbreaks. A Moderna-sponsored Nature Conference, 'Understanding COVID-19 to prepare for the next pandemic', held on the 4–5 April 2022, brought together experts in infectious disease diagnostics, surveillance, vaccine development and therapeutics.

▲ **mRNA vaccines use the host cell to generate the SARS-CoV-2 spike protein.**

CHALLENGES AND LEARNINGS

Over the course of various sessions, they discussed the ongoing challenges and also revelations that could enable a swifter and more focused response to future pandemics.

Participants agreed that vaccines and the gathering of real-world evidence on their effects are vital to end the 'acute' phase of the pandemic, where it continues to be classed as an international emergency. Hopefully we are now heading towards an endemic phase, where the virus will present less of a health emergency as it continues to circulate.

At the conference, two experts from Moderna Inc. in Cambridge, Massachusetts — Jacqueline Miller, Senior Vice President and Therapeutic Area Head, Infectious Diseases; and Paul Burton, Chief Medical Officer — gave presentations on the company's rapidly expanding development pipeline and the central role of real-world evidence in informing public health policy and the development of vaccines.

The success of mRNA COVID-19 vaccines is accelerating the clinical development of many other mRNA vaccines, not just against SARS-CoV-2, but also against other respiratory pathogens, such as influenza and respiratory syncytial virus (RSV).

Miller explained how the ability to rapidly manufacture mRNA vaccines in the laboratory from a DNA template; the willingness of volunteers to participate in clinical trials; and support from national health and regulatory agencies all contributed to Moderna being able to conduct large-scale trials, involving more than 30,000 people. These rapidly led to the approval of its first COVID-19 vaccine in many parts of the world in 2020 and 2021.

REALIZING THE POTENTIAL

Unlike vaccines that rely on live attenuated viruses or a specific virus protein, Moderna's mRNA vaccine carries a single RNA transcript that uses the host cell's machinery to generate the spike protein of SARS-CoV-2. The protein is displayed on the cell surface where it triggers an immune response that protects against future infection.

"Our experiences with the mRNA platform for SARS-CoV-2 vaccines are informing our development activities going forward," Miller said. RNA technology enables a mix-and-match approach to vaccinology, whereby the RNA sequences in a vaccine can be replaced and/or combined to improve their effectiveness against one or more pathogens.

One area Moderna is now focusing on is mRNA vaccines against respiratory viruses such as influenza and RSV, which cause serious infection and have a high economic burden. In the US alone, flu is estimated to cost the economy nearly US$11.2 billion annually[1]. But vaccines against influenza are only 40–60% effective, depending on the age and health of the person being inoculated and how well the vaccine matches the flu viruses spreading in the community[2]. "There is clearly room for improvement," Miller said.

Moderna is also developing a combination vaccine for COVID-19 and flu. It will be tested in healthy adults later this year and its results will be compared to those of standalone mRNA COVID-19 and flu vaccines.

In addition, Moderna is embarking on new programmes to create a COVID-19, flu and RSV combination vaccine and a new pan-coronavirus vaccine. "We are developing various components for combination vaccines, which, ultimately, will improve our preparedness for future pandemics caused by respiratory viruses," Miller explained.

The company's goal is to produce a single, annual, combination vaccine that will reduce the morbidity and mortality caused by many respiratory viruses.

"THIS KNOWLEDGE WILL ALLOW HEALTHCARE SYSTEMS AND GOVERNMENTS TO PREPARE IN A WAY THAT PREVIOUSLY WOULD NOT HAVE BEEN POSSIBLE."

HARNESSING REAL-WORLD EVIDENCE

During the course of the pandemic, the collection of real-world evidence has undergone a revolution. Innovative methods to rapidly and reliably capture data during routine clinical practice, outside the context of controlled clinical trials, have enabled experts to assess vaccine safety and efficacy in real time and make swift decisions about the need for booster doses or changes to vaccine formulations.

"Every day, we have been hearing about how SARS-CoV-2 is impacting our life," said Burton, which has resulted in a "sea-change in our acceptance and understanding of the value of these data."

Real-world evidence is confirming the results of clinical trials, as well as determining the duration of vaccine protection, and their effectiveness against emerging variants. "The analyses, publication and discussion of the data leading to the US Government's decision to provide booster doses in August 2021 happened in only a couple of weeks," Burton explained. This example highlights the speed at which clinical data is shaping health policy and decision-making.

Real-world evidence continues to show that mRNA vaccines and booster doses are reducing the risk of hospitalization and death from COVID-19, even during recent surges of the highly transmissible Omicron variant. It is also providing information on relatively rare events, such as the risk of myocarditis after mRNA-based COVID-19 vaccination[3] and the hospitalization of young children due to infection with SARS-CoV-2 variants. These types of data help public health authorities weigh up the benefits against risk of harm from COVID-19 vaccines.

For example, one recent study looking at the clinical outcome of patients concurrently infected with SARS-CoV-2 and influenza showed that co-infection is associated with increased risk of receiving invasive mechanical ventilation, and death, compared with SARS-CoV-2 infection alone[4]. "As respiratory virus co-infections are more likely as we go into future winters, this knowledge will allow healthcare systems and governments to prepare in a way that previously would not have been possible," Burton said.

Although uncertainties remain about the transition to endemic COVID-19, due to the risk of new variants of concern and waning immunity, he is optimistic. "The transparent dissemination of rigorous real-world evidence and expansion of vaccine manufacturing capacity will not just help shift this pandemic to the endemic phase, but improve our preparedness for new pandemics," he said. ■

SPEAKERS

JACQUELINE MILLER
Senior Vice President, Therapeutic Area Head, Infectious Diseases, Moderna

PAUL BURTON
Chief Medical Officer, Moderna

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MRNA VACCINE TECHNOLOGY BLOOMS ACROSS ASIA-PACIFIC

MRNA LEADER, MODERNA, plans to develop and manufacture mRNA vaccines and therapeutics against many diseases. Rami Suzuki, president of its Japanese subsidiary explains how expanding its operations in Asia is helping it reach these goals.

As many countries adopt a strategy of living with COVID-19, and drop health restrictions that have characterised the pandemic so far, the World Health Organization (WHO) warns that global recovery is dependent on 70% of the world's population being vaccinated[1].

Waning immunity and the emergence of new variants could also hamper recovery it warns. "We need to remain vigilant, hope for the best and prepare for the worst," says Rami Suzuki, Representative Director and President of Moderna in Japan.

In an interview, Suzuki described how Moderna is preparing through the development of variant-specific vaccines and combination vaccines against all SARS-like viruses and other respiratory pathogens. She also emphasized the urgent need to ensure a stable, global supply of COVID-19 vaccines.

To this end, Moderna is establishing long-term strategic partnerships that enable large-scale manufacturing of vaccines and other therapeutics with companies all around the world. "Our goal is to ramp up vaccine production, particularly in countries bearing the highest burden of infectious disease and in those with rapidly ageing populations," she says.

RAMI SUZUKI
President and Representative Director, Moderna Japan

SOLVING HEALTH CHALLENGES

Moderna has existing operations in Australia, South Korea and Japan. The announcement that it is opening new subsidiaries in Hong Kong, Malaysia, Singapore and Taiwan, will help leverage its mRNA vaccine platform to solve health challenges in the Asia-Pacific region.

"It has been an incredible journey," says Suzuki, describing how in just a few years Moderna has gone from being a relatively small, US-based company with no commercial product, to a multinational business with a Japanese subsidiary that will supply nearly 50% of all COVID-19 vaccine doses required in the nation during the second half of 2022. This is just one example of the remarkable global reach of its COVID-19 vaccine.

Suzuki is excited about the company's development pipeline. Moderna now has 46 programmes in development across 43 development candidates, of which 29 are in active clinical trials. Moderna is developing vaccines against viruses for which there are no approved jabs today, she says, including Epstein-Barr Virus (Phase 1), HIV (Phase 1) and Cytomegalovirus (Phase 3). Moderna's technology is also being applied to the development of personalized cancer vaccines and mRNA-based therapeutics for the treatment of heart disease, autoimmune disorders and rare genetic diseases.

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▲ **By opening new subsidiaries in the Asia-Pacific, Moderna hopes to ramp up vaccine production in the region and alleviate supply-chain issues.**

"We are looking for talented scientists that share our dream of transforming human health through mRNA technology", says Suzuki. As well as actively recruiting in Asia, Moderna has launched an 'mRNA Access' program that enables researchers worldwide to use its mRNA vaccine platform to develop vaccines against emerging and neglected infectious diseases in their own labs.

"We are committed to developing vaccines against 15 high-priority targets identified by the WHO by 2025 and to improving the world's preparedness to control the next outbreak or pandemic," she adds.

Speaking about future opportunities, Suzuki highlighted the importance of sharing health data between countries to be able to track and react to emerging trends, on things such as the number of infections and waning immunity, faster and realize Moderna's ambition of collectively improving human health. ■

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