

Moderna Therapeutics

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mRNA vaccines: potential for global impact

A privately held clinical-stage biotechnology company headquartered in Cambridge, Massachusetts, is pioneering messenger RNA (mRNA)-based medicines to transform how the human body prevents and fights disease.

Vaccines to prevent infectious diseases have an enormous impact on public health, and currently protect people against more than 25 different diseases. However, traditional vaccine approaches involve long, complex, and costly development and production processes. As a result, the global health community remains woefully unprepared to address rapidly emerging infectious diseases, as evidenced by the recent epidemics of Zika, Ebola, and chikungunya virus, among others. In addition, many persistent pathogens for which there are no effective vaccines continue to cause widespread sickness worldwide.

Moderna Therapeutics is addressing these challenges by pioneering a new class of vaccines made of mRNA, molecules that carry instructions copied from DNA for the assembly of proteins active in preventing or fighting disease (Fig. 1). The company's mRNA vaccines closely mimic nature by delivering mRNA to the body's cells, which in turn produce antigenic proteins as they would if the body were infected by a virus. The underlying biology of mRNA vaccines enables Moderna to pursue targets that could not be addressed previously.

In addition, unlike traditional vaccines, mRNA vaccines can be rapidly developed, because they do not require dedicated cell-culture-based and/or fermentation-based production of weakened or killed versions of pathogens, inactivated toxins, or partial subunits of the pathogen.

All of Moderna's mRNA vaccines can be produced with a single 'plug-and-play' platform technology and manufactured at a single facility, which enables unprecedented versatility; accelerated research and early-development efforts; efficient, large-scale, standardized production; and a faster response to unanticipated threats.

"In the hundred-year history of vaccinations, mRNA offers a potential new paradigm," said Moderna's CEO Stéphane Bancel. Moderna began operations in 2011, and there are already eight mRNA prophylactic vaccine candidates in the company's pipeline, four of which are involved in clinical studies.

"We continue to invest heavily in our mRNA platform and novel infrastructure to accelerate the pace of R&D because we appreciate the acute global need for a new approach to vaccines and the potential of our mRNA vaccines to prevent disease for millions of people around the world," said Bancel.

Rapid advancement, early progress

One demonstration of the speed with which Moderna's approach can be used to address emergent global health threats is its Zika mRNA vaccine (mRNA-1325), which progressed from idea to first-in-human study in just 12 months. The Zika virus is a

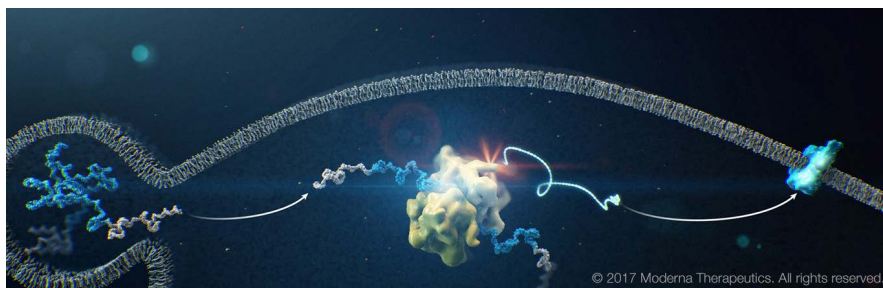


Figure 1: mRNA in action, directing cellular machinery to express a protein.

rapidly emerging pandemic with potential long-term public health implications. Children born to mothers infected with Zika can develop microcephaly, a disease characterized by small, incompletely developed heads, and thus severe disabilities. Zika is also thought to cause the autoimmune condition Guillain-Barré syndrome in adults.

Moderna continues to enroll healthy volunteers in the United States for a phase 1/2 study of mRNA-1325. A funding award from the Biomedical Advanced Research and Development Authority is supporting clinical studies of mRNA-1325.

Phase 1 studies are also under way for two mRNA vaccines that target influenza strains with pandemic potential: mRNA-1440 for influenza A subtype H10N8, and mRNA-1851 for influenza A subtype H7N9. Moderna recently published interim data from its ongoing phase 1 study of mRNA-1440, demonstrating the vaccine's ability to elicit robust immunity in humans with a favorable safety profile¹.

A game changing pipeline

Among the other vaccines currently in development at Moderna is mRNA-1647, an mRNA vaccine for cytomegalovirus (CMV), which is the most common cause of newborn disability and can lead to deafness, microcephaly, vision loss, and mental deficiencies, among other serious complications. It is also the most frequent viral disease in transplant recipients, and often leads to transplant failure. mRNA-1647 combines six mRNAs that encode six different viral proteins: five proteins that constitute the CMV glycoprotein H (gH) pentamer complex, and one other CMV antigen, herpesvirus gB.

Another Moderna vaccine, mRNA-1653, simultaneously targets human metapneumovirus (HMPV) and parainfluenza virus (PIV3). These viruses typically cause mild respiratory illness, but symptoms can become severe in young children, the elderly, and other immunocompromised adults.

With funding from the Defense Advanced Research Projects Agency, Moderna also is developing mRNA-1388, a chikungunya mRNA vaccine.

Currently, there are no approved vaccines for Zika, CMV, HMPV, PIV3 or chikungunya, suggesting the potential global impact that Moderna's mRNA vaccine technology could have.

In collaboration with Merck, Moderna is also conducting a phase 1 study of MRK-1777, an mRNA vaccine for an undisclosed viral indication. Moderna and Merck have a strategic collaboration to discover and develop mRNA-based vaccines and passive immunity treatments for viral diseases. The two companies also are partnering to advance mRNA-based personalized cancer vaccines in combination with Merck's anti-PD-1 therapy, Keytruda (pembrolizumab).

Moderna is partnering with the Bill & Melinda Gates Foundation to develop an mRNA antibody combination to help prevent human immunodeficiency virus (HIV) infection. Moderna's global health partnership with the foundation may also include additional mRNA-based development projects for various infectious diseases, with total funding of up to \$100 million.

Beyond mRNA vaccines, Moderna is advancing mRNA therapeutics for cardiometabolic disease, immuno-oncology, and rare diseases, among other indications. The company also has existing partnerships with AstraZeneca, Alexion Pharmaceuticals and Vertex Pharmaceuticals.

"We're very grateful to our partners," Bancel said. "Their support and therapeutic area expertise are enabling us to explore the expansive potential of mRNA medicines to address a broad spectrum of significant unmet needs."

1. Bahl, K. et al. *Mol. Ther.* <http://dx.doi.org/10.1016/j.jymthe.2017.03.035> (2017).

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