mRNA Innovation Is Revolutionizing Disease Prevention

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*This article was originally published on **This Month in Transformative Medicine** on July 5, 2023. **Anshul Mangal**, President of Project Farma & Precision ADVANCE and **Chad Salisbury**, Senior Vice President of Project Farma (PF), discuss the mRNA revolution and its impact on the future of disease prevention and treatment.*

While mRNA technology gained its claim to fame through the vaccines developed during the coronavirus pandemic, researchers are determined to prove its potential extends far beyond COVID.

The first FDA approved mRNA product was decades in the making, following many iterations throughout history the first mRNA vaccine in the US was brought to life. This achievement delivered aid to patients and healthcare providers during the most critical public health crisis in recent years. Since then, researchers have been operating at incredible speeds to develop more novel mRNA treatment options for patients, across many indications.

With recent advancements, we can now encode an mRNA molecule with specific instructions, safely deliver it to a cell, and see it carry out the desired function - forever changing the landscape of personalized medicine. Until very recently, a patient born with a hereditary disease had limited access to meaningful treatment options. By leveraging the potential of mRNA technology, we have now seen that it's possible to help our bodies carry out natural functions as they're intended to, regardless of our genetic makeup.

The Storied History of mRNA

mRNA's story began long before the pandemic, researchers have been working to understand how this molecular messenger could be delivered and introduced into the cells since the 1970s. Early research was marked with much excitement but encountered significant obstacles. The biggest hurdle preventing the application of this technology was the degradation of the mRNA in the body before it could deliver its message, ultimately preventing the target proteins from being created. Advancements came with the development of lipid nanoparticles that would eventually envelope the mRNA to improve delivery and uptake by the body and ultimately allowing the mRNA to enter the cells for protein synthesis. The first mRNA vaccine to leverage the fatty delivery mechanism was used overseas to fight the Ebola virus. In 2021, the culmination of a 30-year effort, Pfizer's COVID-19 vaccine was the first mRNA product to receive full FDA approval in the US.

mRNA's big differentiator is that its composition is free of viral particles. Most viral vaccines leverage the weakened virus or pieces of it to help the immune system recognize and form a response. Rather than use the virus itself, mRNA vaccines teach our cells to make the spike protein that is found on the surface of the virus to train the immune system to recognize and make antibodies before you're ever infected. The body can then recognize, neutralize, and destroy incoming virus particles.

Scientists can now engineer a specific mRNA molecule with a message and safely deliver it to a cell to carry out the specific instructions it was encoded with. This same technology and concept can be applied to address underlying causes of diseases as well as cancer cells to be recognized and destroyed before they spread.

Breaking Barriers: How the mRNA Revolution is Unfolding Today

Following the resolution of the COVID-19 pandemic, many companies are looking to expand their offerings and use of mRNA technology beyond the coronavirus vaccine.

Moderna: The mRNA Pioneer
Now that demand for their COVID vaccine has dwindled, mRNA pioneer Moderna is expanding their internal capacity **with the purchase of a second plant** in Massachusetts and have their sights set beyond COVID into other vaccines including influenza and immuno-oncology products.

As the COVID pandemic and therefore need for the vaccine winds down, Moderna is experimenting with mRNA technology to treat rare diseases through the **replacement of intracellular proteins**. The company is conducting a Phase 1/ 2 trial for children suffering from a rare inherited metabolic disorder called propionic acidemia (PA). The disorder is caused by a deficiency in a critical enzyme called propionyl-CoA carboxylase. This enzyme is required for the proper breakdown of amino acids, that if built up in the body can lead to life threatening metabolic decompensation events.

Moderna's mRNA-3927 is a lipid nanoparticle-encapsulated dual mRNA protein replacement therapy that is encoded to instruct the body to create the two proteins, PCCA and PCCB, that form the propionyl-CoA carboxylase patients with this disorder are naturally deficient in. By coding for these proteins, the enzyme can carry out its function to prevent the buildup of harmful compounds that cause PA symptoms and can ultimately treat the underlying cause of the disease.

Participants in the trial suffered fewer PA related events after starting on the therapy, with Moderna tracking a 66% overall relative risk reduction across the trial and a 78% reduction in the four cohorts that received mRNA-3927 every two weeks.

Moderna has now given over 280 doses of the treatment and has had 5 patients on the therapy for more than a year, the study did not see any dose limiting toxicities and is now entering the dose expansion phase. Moderna's trial is the first time a biotech has reported clinical data on mRNA therapeutic for intracellular protein replacement and is an exciting development for the future applications of mRNA technology.

Moderna's goals and aspirations have long been to harness the power of mRNA and with the latest developments, are more confident than ever the technology will forever change how we treat cancers.

Innovation for Pancreatic Cancer

Pancreatic cancer is one of the deadliest forms of cancer and is currently the third leading cause of death in the US, with prevalence rising. Pancreatic ductal adenocarcinoma is the most common type of pancreatic cancer and has a mortality rate of 88%. The current standard of care includes surgery and chemotherapy but are only partially effective as the cancer has a 90% recurrence rate around 7-9 months. Other treatments like immunotherapy are largely ineffective, leaving patients diagnosed with this devastating cancer with extremely limited options and little hope.

Pancreatic cancer goes undetected until the later stages as the cancer proteins, known as neoantigens, are not as recognizable by the body's T-cells and general immune response. Scientists have noted that of those patients who do survive pancreatic cancer have T-cells that naturally elicit a stronger response to the neoantigens and have leveraged this fact to test out a new treatment option.

In an exciting **new publication** researchers detailed their findings in a small study of patients with pancreatic cancer who received a novel mRNA vaccine aimed at treating their aggressive cancer. 16 patients underwent surgery and received the novel vaccine, half of which did not have tumor recurrence after surgery. 18 months later those patients were still tumor free!

The vaccines were personalized to each patient's cancer, with an mRNA scripted to target their specific tumor's neoantigens to help T-cells recognize and attack the cancer cells. The vaccines were developed in about 9 weeks, which is critical as time is of the essence for patients that are diagnosed at later stages.

The vaccine was given in combination with an adjuvant to increase the effects and chemotherapy, so it is difficult at this stage to understand how much of the results were attributed to the vaccine alone. While these results are not considered definitive proof and will need to be replicated in larger studies, these early results are promising. In the other 8 patients that saw recurrence, the cancer returned after a year. However, given the recurrence rate, timeline, and ultimately grim prognosis of pancreatic cancer any progress is extremely exciting for patients that currently have limited treatment options.

A Universal Flu Vaccine

In other exciting developments harnessing the power of mRNA platforms for vaccines. The National Institute of Allergy and Infectious Diseases' (NIAID) Vaccine Research Center (VRC), part of the National Institutes of Health, have developed an experimental **universal flu vaccine** that leverages an mRNA platform.

Currently, the seasonal flu vaccines aim to protect against 4 strains of flu which are predicted by scientific experts based upon an extensive global influenza surveillance network. While strain recommendations are made twice a year by the World Health Organization, influenza viruses are continuing to mutate over the course of long production timelines, potentially rendering the vaccines less effective to the circulating strains at the time of vaccination. The concept behind a universal flu vaccine would hopefully cover a wider range of strains and would not require annual vaccination. Researchers behind the vaccine are also hopeful that it could offer greater protection against future influenza pandemics.

A clinical trial has begun enrolling patients in a Phase I trial at Duke University to test the vaccine's safety and ability to produce an immune response. Researchers are testing against the seasonal vaccine to measure safety and efficacy against the current standard. It is the first investigational universal flu vaccine candidate to be tested by the CIVICs program and was manufactured at the facilities of CIVIC'S Duke Human Vaccine Institute (DHVI).

The novelty of the universal flu vaccine compared to the current seasonal vaccine is in the specific portion of the viral particle leveraged to invoke an immune response. The universal vaccine uses the stem of the flu protein hemagglutinin (HA) to induce a broader immune response against influenza virus. In the virus particle the HA head changes as the flu virus spreads and evolves, making it more difficult to create immunity against. While the HA stem is more stable, evolves slowly over time and is similar across many different types of the flu virus. By leveraging this portion of the protein, developers might be able to provide longer term immunity to a wider range of strains.

In parallel to the pursuit for a universal flu vaccine, mRNA vaccine innovators like Pfizer and Moderna have ongoing clinical trials for seasonal influenza vaccine candidates using the mRNA platform, in combination with the circulating COVID strain, to enable a single annual vaccination to protect public health. The mRNA platform provides a shorter time to market as compared to existing influenza vaccine platforms. This could allow scientific experts to have additional time to gather virus surveillance data prior to making strain recommendations. Infectious diseases such as COVID and influenza are just beginning to show the potential for how this platform can be positioned to improve public health.

The Future of mRNA

mRNA became a household name through vaccines, but there is much to be discovered with how the manipulation of this powerful technology could change **the future** of disease treatment. **Companies** are now prioritizing exploration in this space to find new ways to treat everything from HIV, influenza, autoimmune, and other diseases that have gone without significant innovation.

As researchers aspire to unlock the full power of mRNA technologies, we will begin to see how this platform could play a role in revolutionizing the treatment of rare diseases and individualizing how we treat cancers. By arming patient immune systems with the tools to fight threats and create critical but deficient proteins, we have truly opened a world of new possibilities for patients everywhere.

It is imperative that these innovative solutions are supported, brought to life and can ultimately reach the patients who need them. Through innovation and determination our industry has swiftly overcome obstacles to unleash the power of mRNA platforms and the full potential of this technology has yet to be realized.

About the Authors

Anshul Mangal
Anshul Mangal is President of Project FARMA & Precision ADVANCE. Anshul founded and grew PF into a leading global biologics and advanced therapy engineering consulting firm. Under Anshul's leadership, PF pioneered the industrialization of advanced therapies including two notable, commercially approved cell and gene therapies. PF was acquired by Precision Medicine Group in 2020 to be the cornerstone of Precision ADVANCE. ADVANCE is a collection of Precision's services uniquely focused on the complexities of research and clinical development, regulatory, manufacturing, and commercial needs to successfully bring an advanced therapy to market.

Chad Salisbury

Chad Salisbury joined Project Farma in October 2022 as Senior Vice President of Technical Operations. Chad has over 20 years of Technical Operations and Quality experience encompassing gene therapy, vaccines, sterile injectables and small molecules, including the delivery of ~$2B USD of greenfield cGMP manufacturing facilities. His experience includes full life cycle management of both mammalian cell culture operations and parenteral fill finish operations from design/ CQV through startup and ongoing commercial operations. Chad has a proven track record with successful delivery of six new product introductions including three blockbusters. Chad has held increasingly responsible management positions in manufacturing, quality, engineering and supply chain. Chad was most recently VP, Manufacturing at Affinia Therapeutics, a company singularly focused on using innovations in gene therapy to lead the fight against devastating rare and prevalent diseases. Prior to Affinia, Chad held progressive roles at CSL Seqirus, Novartis and Eli Lilly in both the US and Europe.

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