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# What does the success of mRNA vaccines tell us about the future of biological therapeutics?

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## mRNA: A novel drug class

For more than a decade, mRNA has been evaluated as a potential cancer vaccine in human trials; but selecting the right antigens to lead to tumor shrinkage remains a considerable challenge. However, the recent success of COVID-19 mRNA vaccines demonstrates the power of mRNA-based therapeutics, the platform's adaptability, universality, short manufacturing time, and ease in scaling up.

We are already seeing a host of mRNA vaccines against other pathogens enter the pipelines, as well as mRNA encoding antibodies for passive immunization to prevent or treat various infectious diseases. Clinical trials are also underway, utilizing mRNA encoding therapeutic proteins to combat cancer by making cold tumors hot and to reverse vascular dysfunction in the heart or in the wounds of diabetics. Animal models of multiple sclerosis have confirmed that tolerization can be achieved with mRNA therapy, thus opening the possibility to treat autoimmune diseases. Encouraging clinical trial results were recently reported on genome editing with Cas9 mRNA delivered into the liver for the treatment of transthyretin amyloidosis, revealing the potential of mRNA for fulfilling the promise of gene therapy and permanently curing genetic diseases.

Further developing formulations to deliver Cas9 mRNA into stem cells of the bone marrow will expand therapeutic application of mRNA to cure many other diseases, such as HIV and sickle-cell disease by *in vivo* genome editing. The potential of mRNA therapy seems unlimited.

**Kathryn Whitehead**
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## mRNA drugs are here to stay

The future of RNA-based therapeutics is bright! For years, RNA drugs have been regarded with excitement because of their broad therapeutic potential and skepticism due to concerns about immunogenicity. Although Alnylam broke through with the first approved siRNA drug in 2018, cynicism remained for mRNA because the immune response to exogenous mRNA often inhibits protein expression. Fortunately, Kati Karikó and others pioneered nucleoside modification and sequence design strategies that enable robust protein expression *in vivo*. Now, Moderna, Curevax, Arcturus, and other companies have mRNA therapeutics and vaccines in clinical trials, with early successes reported.

However, this was still a niche technology until the pandemic hit, but in our desperation, we were open to something new. So far, the SARS-CoV-2 mRNA vaccines have been a spectacular success; and now, we're collecting long-term safety and efficacy data in millions of people. So long as these data continue to look positive, the barrier to lipid nanoparticle and RNA therapies will be substantially reduced. Within the next several decades, we'll likely have treatments for hemophilia, sickle-cell anemia, and other rare diseases. We'll likely have vaccines against numerous infectious pathogens and maybe even a universal flu vaccine. All of this will continue to depend on nanoparticles that take the mRNA to the right cells; so drug delivery scientists like me should be in business for a very long time.

**Roy van der Meel**
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## Delivering next-gen therapeutics

COVID-19 mRNA vaccines' tremendous success has highlighted the crucial role of lipid nanoparticle (LNP) technology. Initially developed for therapeutic gene silencing in hepatocytes by delivering small interfering RNA to the liver, LNPs protect mRNA from degradation and facilitate its intracellular delivery. In addition to phospholipids and cholesterol and polyethylene glycol lipids, LNPs contain ionizable cationic lipids that ensure efficient mRNA encapsulation while maintaining neutral charge at physiological pH and promoting endosomal escape.

Although the versatile LNP-mRNA technology's power lies in its ability to dramatically accelerate the response time to (future) viral pandemics, its near-future applications likely include treatments for established infectious diseases such as malaria or a universal influenza vaccine. As a result, one of its original applications, i.e., truly personalized cancer immunotherapies based on mRNA vaccines encoding individual cancer-specific neoepitopes, will gain a lot of momentum. Beyond vaccine approaches, intravenously administering LNP-mRNA can convert the liver into a 'bioreactor' for therapeutic protein production, e.g., for treatment of hemophilia or metabolic disorders. Excitingly, owing to their ability to deliver large nucleic acid payloads, LNPs are now also enabling *in vivo* gene editing. LNP-mediated delivery of mRNA encoding base editors and single-guide RNA targeting *PCSK9* resulted in stable reduction of cholesterol levels in non-human primates. Very recently, Gillmore and colleagues reported in the *New England Journal of Medicine* how a single dose of LNP-mRNA encoding Cas9 and single-guide RNA targeting *TTR* resulted in durable knockout in humans.

As LNP technology is enabling the next generation of therapeutics, important challenges—such as infusion-related effects, immunogenicity, and delivering to extrahepatic tissues following intravenous administration—must be overcome.