mRNA Technologies: A Primer

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mRNA Technologies: A Primer

SUMMARY

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Decades of research on messenger RNA (mRNA) and related technologies enabled the rapid development of the Pfizer/BioNTech and Moderna Coronavirus Disease 2019 (COVID-19) vaccines. Some experts believe that this success portends a revolution in medicine that will bring better pandemic preparedness and new treatments for disease. This rapid progress may present questions for congressional consideration. For example, what is the appropriate role for the federal government in supporting and coordinating mRNA-related research and development (R&D)?

Messenger RNA is a biological molecule whose central role in cellular protein production makes it an attractive target for a host of medical treatments and vaccines. The COVID-19 mRNA vaccines represent the first Food and Drug Administration-approved uses of mRNA-based technology. Vaccines against Human Immunodeficiency Virus (HIV), rabies, and influenza and treatments for cancer and certain rare diseases are in clinical trials. At the same time, mRNA research and the development of other, more-wide ranging, uses of this technology face challenges, including potential undesired immune responses to repeated treatments, complications with targeting the appropriate tissue, and the need to protect the mRNA from premature degradation. The federal government, largely through the National Institutes of Health (NIH) and the Defense Advanced Research Projects Agency (DARPA), has invested billions of dollars in R&D of mRNA and related technologies.

Despite the research challenges facing further commercial applications, several groups project mRNA-related revenue to increase by a compound annual growth rate of between 10% and 90% over the next 5 to 10 years. Consistent with these growth projections, private investments are being made by and in companies of varying size and technology maturity that are conducting mRNA R&D.

The potential future benefits of mRNA technology and the lessons learned during past R&D on this technology raise some possible issues for Congress:

- In addition to funding the foundational basic research that led to this technology, the federal government shifted its support during the COVID-19 pandemic to include activities generally left to the private sector, such as late-stage clinical trials and research, product development, and manufacturing. The appropriate role of the federal government in late-stage R&D is not a new issue; however, the pandemic would mark an inflection point if Congress were to continue increased support for such activities.
- The difficulty faced by some researchers in obtaining funding for what, in retrospect, were crucial fundamental studies raises questions about whether NIH's committee-based peer review process adequately funds "high-risk, high-reward" projects. Support for high-risk, high-reward research is considered an important element in developing breakthrough technologies that address societal challenges, including health-related challenges, and in maintaining the economic competitiveness of the United States. Congress may have already taken steps to address this through the $1 billion it appropriated for FY2022 to establish the Advanced Research Projects Agency for Health (ARPA-H) in the Department of Health and Human Services (HHS). ARPA-H is modeled after DARPA in its approach to funding high-risk, high-reward research.
- Apart from directly setting the level of support for mRNA technology R&D, Congress may consider options such as facilitating coordination of this research or providing for a technological research plan.
- If the U.S. seeks to maintain its global leadership role in the life sciences broadly, and in mRNA technologies specifically, then Congress would likely face consideration of how to ensure the implementation of robust federal policies, which may include increased federal R&D funding; an effective regulatory environment; a well-trained and adequate life sciences workforce; and public and private sector coordination.

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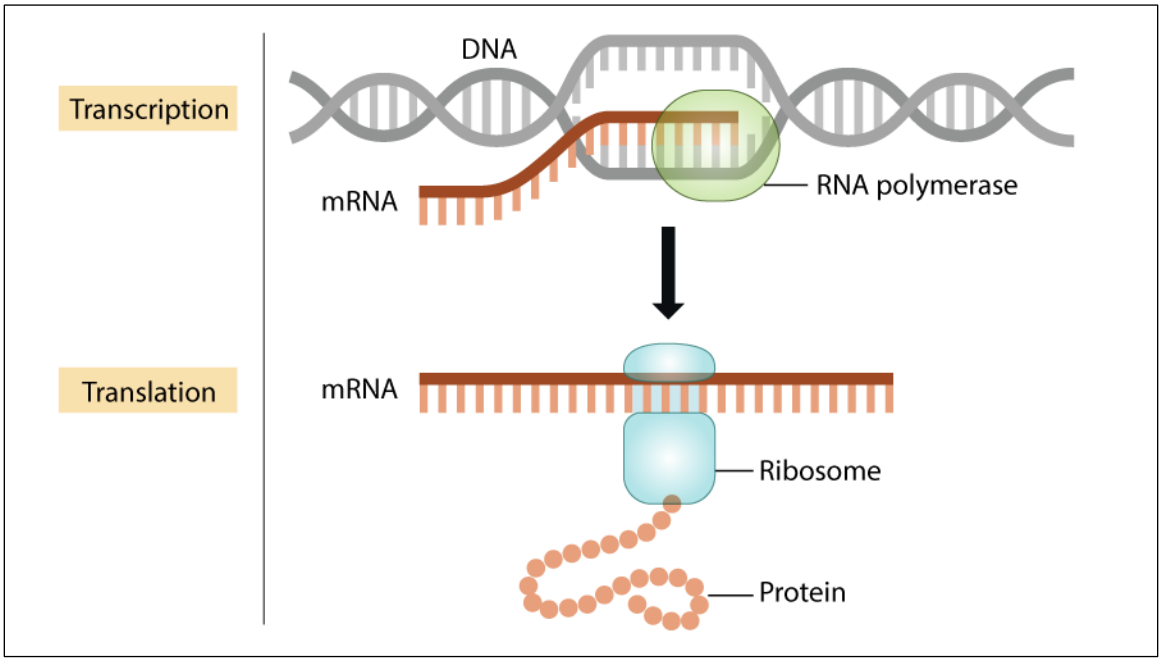
Introduction

The unprecedented development speed of the Pfizer/BioNTech and Moderna Coronavirus Disease 2019 (COVID-19) vaccines highlight just one application of emerging technologies based on messenger RNA (mRNA), which have many promising uses and benefits. In addition to enabling rapid vaccine development for emerging infectious diseases, these technologies may soon have wider application in preventing and treating other diseases. This report discusses what mRNA is and why it has so many potential uses; how the federal government and private companies developed these technologies; federal and other investments in research and development (R&D) related to these technologies; future potential uses; and congressional considerations raised by these technologies.

What Is mRNA?

Ribonucleic acid (RNA) is a macromolecule found in all living cells. Cells use RNA for many functions, including in protein production. A particular type of RNA, messenger RNA (mRNA), is so named because it conveys protein-encoding information stored in the cell's DNA (deoxyribonucleic acid) to the protein production machinery of the cell. (See **Figure 1**.) Enzymes called RNA polymerases "transcribe" the DNA sequence into an mRNA sequence. Then ribosomes produce specific proteins by linking amino acids in the order directed by the mRNA sequence, a process known as "translation."

Figure 1. The Role of mRNA in Protein Production



Source: CRS.

Notes: In correspondence to a DNA sequence, the RNA polymerase enzyme links RNA bases together to form an mRNA sequence. The mRNA disengages from the DNA strand and travels to a ribosome, which in correspondence to the mRNA sequence, links amino acids together to form a protein.

mRNA-based Medicine

Because of its central role in protein production, mRNA is an attractive target for manipulating the proteins a cell makes without having to alter the cell's DNA. Adding the appropriate mRNA to a cell can cause it to make a specified protein. This can be useful in treating and preventing many diseases. To develop the ability to do this, scientists had to work for decades to overcome many technical hurdles before realizing the promise of mRNA technology through its first successful commercial applications, the Pfizer/BioNTech and Moderna COVID-19 vaccines. (See **Figure 2**.)

Since the discovery of mRNA in the 1960s, researchers have expanded their understanding of how it works and its potential role in the treatment and prevention of human disease. Early research focused on understanding the structure and function of mRNA and its metabolism in cells. In the late 1960s and early 1970s, scientists were able to produce proteins from mRNA isolated in the laboratory. In 1984, scientists synthesized mRNA in the laboratory for the first time. In the early 1990s, scientists reported the first successful uses of mRNA in rodents as a treatment and as a vaccine. For example, in 1992, scientists caused rats to produce a hormone by injecting the appropriate mRNA. In 2005, scientists were able to overcome one of the major hurdles preventing the widespread use of mRNA as a therapeutic—the triggering of an immune response. This was achieved by modifying the synthetically produced mRNA. The first human clinical trials for mRNA-based vaccines began in 2014 (rabies) and 2015 (influenza).

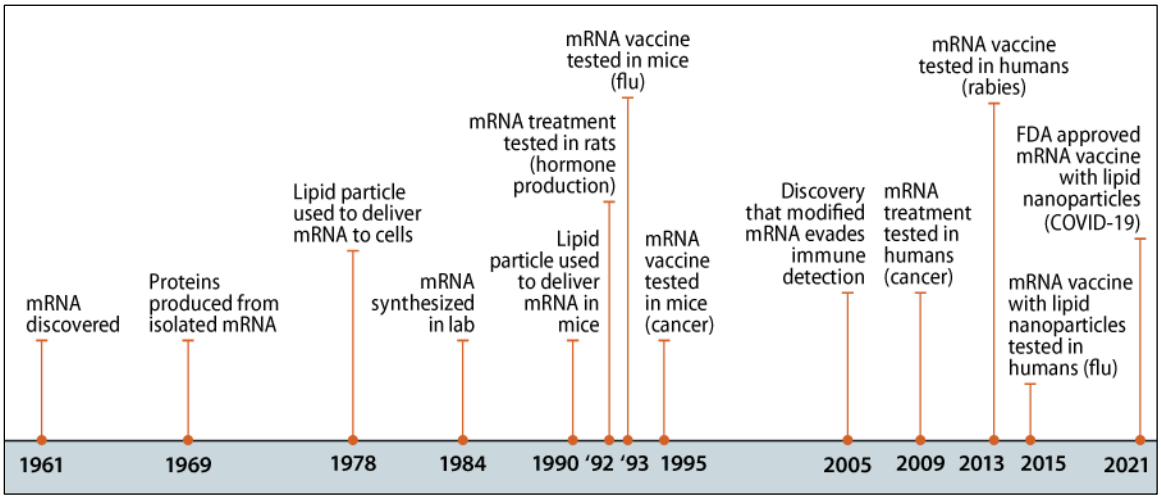
The first Food and Drug Administration (FDA)-approved human uses for mRNA were the 2021 approvals of the COVID-19 vaccines by Pfizer/BioNTech and Moderna. Their success relied on breakthroughs in protecting mRNA from degradation and in using precisely formulated lipid nanoparticles (see text box, "Lipid Nanoparticles"). In contrast to other vaccines that rely on injecting premade antigens—substances that cause the body to formulate an immune response—mRNA-based vaccines cause cells to make the antigens themselves. In the case of the COVID-19 vaccines, the delivered mRNA encodes for a modified spike protein on the surface of the SARS-CoV-2 virus (which causes COVID-19). In other words, the COVID-19 mRNA vaccines cause a person's cells to make one modified viral protein, which can trigger an immune response to protect against future exposures to the virus.

Lipid Nanoparticles

Lipid nanoparticles are small bubbles of fat that can be used to encapsulate mRNA. This encapsulation can help protect the mRNA from degradation before it reaches the targeted cells. Precisely controlling the types of lipids and other chemicals used to produce the nanoparticles can maximize the amount of mRNA delivered to the targeted cells and thus increase the chance that the cell will produce the desired protein. Both successful mRNA-based COVID-19 vaccines relied on precisely formulated lipid nanoparticles.

One of the most promising aspects of mRNA-based medicine is the relative ease of creating the mRNA. In particular, it is relatively easy to produce at commercial scale and has the potential to increase the adaptability of medical interventions, especially of vaccines. Producers of mRNA-based vaccines can more easily modify their vaccines to account for antigen drift—genetic changes in a virus that produce a new strain—than traditional vaccine producers. For example, if new strains of SARS-CoV-2 virus arise that are vaccine resistant because of changes to the spike protein, mRNA vaccine manufacturers can adjust their mRNA and begin producing an updated vaccine more quickly than manufacturers of other types of vaccines.

Figure 2. Select mRNA Research Milestones



Source: CRS, modified from Elie Dolgin, "The Tangled History of mRNA Vaccines," *Nature*, vol. 597 (September 16, 2021), p. 323; and Ugur Sahin, Katalin Kariko, and Ozlem Tureci, "mRNA-Based Therapeutics-Developing a New Class of Drugs," *Nature Reviews Drug Discovery*, vol. 13 (October 2014), pp. 760-761.

Potential Future Uses

While scientists have long recognized the potential of RNA-based therapeutics, the rapid development of mRNA-based COVID-19 vaccines has renewed interest and increased investment in such technologies. Future mRNA technologies include new mRNA-based vaccines (both prophylactic/preventative and therapeutic vaccines), as well as non-vaccine therapies. The following sections provide illustrative examples of the potential uses of mRNA technologies currently being explored, in addition to outlining some challenges associated with their development.

Other mRNA-Based Vaccines

As do COVID-19 vaccines, other mRNA-based vaccines seek to trigger a prophylactic or protective response to a known virus (e.g., Zika, shingles, influenza) through the use of synthetic mRNA. The synthetic mRNA serves as the template for the production of viral proteins that activate the body's immune system and the production of antibodies. As long as the vaccine induces a sufficient immune response, when a person is subsequently exposed to the targeted virus then the antibodies will recognize it and help the immune system identify and eliminate the virus before it can cause illness (or severe illness).

Human Immunodeficiency Virus (HIV)

In January 2022, the International AIDS Vaccine Initiative (IAVI) and Moderna began a Phase I clinical trial for an mRNA-based HIV vaccine.[1] HIV is a fast-evolving virus that has been difficult to target effectively because of the number and diversity of HIV strains. Many scientists consider stimulating the production of broadly neutralizing antibodies as the key to developing an

[1] Clinical trials are typically divided into three sequential categories or phases. Phase I tests safety and dosage. Phase II tests effectiveness and side effects. Phase III tests effectiveness and adverse effects in a larger population. For more information, see CRS Infographic IG10013, *The Pharmaceutical Drug Development Process*, by Agata Bodie and Kavya Sekar.

effective HIV vaccine. The production of broadly neutralizing antibodies will likely involve sequential vaccinations, and the use of an mRNA-based vaccine platform has the potential to reduce development times dramatically for such vaccines. According to IAVI and Moderna, the purpose of the trial is to determine whether the mRNA vaccine platform can safely and effectively generate a specific immune response (i.e., a rare class of B cells) that is considered the first step in the process of inducing broadly neutralizing antibodies to HIV.[2]

Rabies

In January 2020, CureVac reported positive results associated with a Phase I clinical trial for an mRNA-based rabies vaccine.[3] Specifically, all 53 study participants produced antibodies at a level above the threshold recommended by the World Health Organization (WHO). According to the WHO, most cases of rabies occur in Africa and Asia, with 40% of cases occurring in children under the age of 15. The WHO and others are seeking to achieve zero human deaths from dog-transmitted rabies bites by 2030.[4]

Influenza

Several companies, including Pfizer, Moderna, CureVac, and Sanofi, are in the process of developing mRNA-based influenza vaccines. Given the burden of seasonal flu, such companies were already focused on creating new influenza vaccines before the COVID-19 pandemic.[5] Many see the potentially shorter development time and flexibility associated with mRNA-based vaccine platforms as being advantageous in addressing the flu, which is caused by four different types of influenza viruses (A, B, C, and D) with many strains that are constantly changing.[6] Current influenza vaccines—based on inactivated viruses or recombinant proteins—are generally 40% to 60% effective in preventing infection; it remains to be seen whether mRNA-based flu vaccines would have greater efficacy.[7]

Cancer Treatments

In general, the primary difference in the use of mRNA-based vaccines for cancer compared to infectious disease (e.g., COVID-19, influenza) is that they are therapeutic vaccines, meaning the goal is treatment, not prophylaxis. That is, the synthetic mRNA triggers the immune system to identify and attack cancer cells that already exist in the patient, rather than teaching the immune

[2] IAVI, "IAVI and Moderna Launch Trial of HIV Vaccine Antigens Delivered through mRNA Technology," press release, January 27, 2022, https://www.iavi.org/news-resources/press-releases/2022/iavi-and-moderna-launch-trial-of-mrna-hiv-vaccine-antigens.

[3] CureVac, "CureVac Announces Positive Results in Low Dose—1 µg—Rabies Vaccine Clinical Phase 1 Study," press release, January 7, 2020, https://www.curevac.com/en/2020/01/07/curevac-announces-positive-results-in-low-dose-1-%C2%B5g-rabies-vaccine-clinical-phase-1-study/.

[4] World Health Organization, *Rabies Vaccines: WHO Position Paper*, April 2018, https://apps.who.int/iris/bitstream/handle/10665/272372/WER9316-201-219.pdf.

[5] The U.S. Centers for Disease Control and Prevention (CDC) estimates that seasonal flu resulted in 9 million to 41 million illnesses, 140,000 to 710,000 hospitalizations, and 12,000 to 52,000 deaths annually between 2010 and 2020. According to the CDC, "it uses the estimates of the burden of flu in the population and the impact of flu vaccination to inform policy and communications related to flu." (CDC, "Disease Burden of Flu," https://www.cdc.gov/flu/about/burden/index.html)

[6] Elie Dolgin, "mRNA Flu Shots Move into Trials," *Nature Reviews*, vol. 20, November 2021, pp. 801-803.

[7] Derek Lowe, "Moderna's mRNA Flu Vaccine," December 10, 2021, at https://www.science.org/content/blog-post/moderna-s-mrna-flu-vaccine.

system to identify and attack a virus that a patient may later be exposed to. Several biopharmaceutical companies are pursuing the development of mRNA-based cancer treatments for a variety of different cancers. For example, BioNTech is developing cancer treatments that target common molecules associated with cancer cells across patients with a particular type of cancer, in addition to developing treatments that identify and target cancer mutations that are unique and specific to a patient (i.e., personalized cancer treatments). Both treatments would help the patient's immune system identify and attack cancer cells by providing synthetic mRNA as a template for the production of antibodies. BioNTech is conducting clinical trials on its broader or more generalized mRNA-based cancer vaccines for advanced melanoma, prostate cancer, head and neck cancer, and ovarian cancer. It is conducting clinical trials on its personalized cancer vaccines for colon cancer, solid tumors, and melanoma.[8]

Rare Diseases

Messenger RNA technologies also have the potential to treat patients with rare genetic diseases or other disorders associated with missing or dysfunctional proteins. Similar to the potential uses described above, synthetic mRNA introduced into a patient's body would serve as a template for the production of the missing or dysfunctional protein that is the cause of the rare disease or disorder. For example, Arcturus Therapeutics is in the process of initiating a Phase Ib clinical trial to use mRNA to treat Ornithine Transcarbamylase (OTC) Deficiency. OTC is a liver enzyme that removes ammonia from the body; if ammonia accumulates it can cause diminished cognitive ability, seizures, coma, and death. The clinical trial seeks to determine the safety and tolerability of the mRNA treatment, which has the goal of increasing OTC levels in study participants.[9] In another example, Moderna is initiating a Phase I/II clinical trial to treat elevated levels of methylmalonic acid which are caused by a deficiency or defect in one of the enzymes responsible for breaking down the acid. High levels of methylmalonic acid can cause drowsiness, coma, and seizures, among other long-term consequences. The clinical trial seeks to determine the safety of the mRNA treatment, which has the goal of increasing the amount of enzymes that break down methylmalonic acid in study participants.[10]

Research Challenges

While mRNA technologies may have the potential to revolutionize medicine, challenges remain in unlocking their full potential.[11] In particular, the use of mRNA technologies to treat chronic or genetic diseases would typically require repeated doses to replace a missing or defective protein over a patient's lifetime as the mRNA is degraded over time. Repeated dosing could trigger the body's immune response and lead to adverse reactions and side effects. There is also a possibility that the effectiveness of a treatment could wane over time. In addition, there is a need to improve

[8] Derek Thompson, "Maybe the Coronavirus Was Lower-Hanging Fruit," *The Atlantic*, October 18, 2021, https://www.theatlantic.com/ideas/archive/2021/10/mrna-vaccines-cure-cancer-biontech/620383/; Kaitlin Sullivan, Reynolds Lewis, and Akshay Syal, "Could mRNA Vaccines Be the Next Frontier of Cancer Treatment?," NBC News, https://www.nbcnews.com/health/cancer/mrna-vaccines-frontier-cancer-treatment-rcna8886; BioNTech, "Pipeline," at https://biontech.de/science/pipeline; and BioNTech, "Platforms," at https://biontech.de/science/platforms.

[9] "Safety, Tolerability, and Pharmacokinetics of ARCT-810 in Stable Adult Subjects with Ornithine Transcarbamylase Deficiency," NCT04442347, https://clinicaltrials.gov/ct2/show/NCT04442347.

[10] "A Study to Assess Safety, Pharmacokinetics, and Pharmacodynamics of mRNA-3705 in Participants with Isolated Methylmalonic Acidemia," NCT04899310, https://clinicaltrials.gov/ct2/show/NCT04899310.

[11] See, for example, Mary Bates, "The mRNA Revolution Is Coming," *IEEE Pulse*, November/December 2021, https://www.embs.org/pulse/articles/the-mrna-revolution-is-coming/; and Kelly Servick, "Messenger RNA Gave Us a COVID-19 Vaccine. Will It Treat Diseases, Too?," *Science*, December 16, 2020, https://www.science.org/content/article/messenger-rna-gave-us-covid-19-vaccine-will-it-treat-diseases-too.

methods for delivering mRNA drugs or therapeutics to targeted cells or tissues to enable effective treatment. Finally, the stability of mRNA remains an issue. It requires special cold-chain storage and handling before use. Additionally, once injected, it is actively degraded by the body, but will need to persist long enough to have the desired effect. The success of the mRNA-based COVID-19 vaccines reflects the ability of the research community to overcome these challenges, but they remain key issues if mRNA technologies are to be expanded beyond their use in vaccine development.

Federal Support, Market Projections, and Private Investment

This section discusses federal support for mRNA R&D and related activities (e.g., manufacturing facilities), recent projections made by market research firms, and selected private investments related to mRNA technologies.

Federal Support

The success of the mRNA-based COVID-19 vaccines relied on decades of federally supported research and development on mRNA and lipid nanoparticles, primarily through the National Institutes of Health and the Defense Advanced Research Projects Agency.

Although NIH—the primary federal agency charged with performing and supporting biomedical research—has not reported the amount it invested in this development, a group of university researchers has estimated that between 2000 and 2019 NIH directed approximately $950 million towards mRNA vaccines and $500 million towards lipid nanoparticles.[12]

DARPA also contributed to the development of these technologies. Between 2011 and 2020, DARPA invested approximately $400 million through the Autonomous Diagnostics to Enable Prevention and Therapeutics (ADEPT) program and the Pandemic Prevention Platform (P3) program.[13] The objective of the ADEPT program was to support "individual troop readiness and total force health protection by developing technologies to rapidly identify and respond to threats posed by natural and engineered diseases and toxins," including "novel methods for rapidly manufacturing new types of vaccines."[14] In 2011, through the ADEPT program, DARPA started investing in the development of nucleic acid vaccines.[15] The P3 program, an outgrowth of the ADEPT program, "focuses on rapid discovery, characterization, production, testing, and delivery of efficacious DNA- and RNA-encoded medical countermeasures," including vaccines.[16]

During the COVID-19 pandemic, the Biomedical Advanced Research and Development Authority (BARDA), an office in the Department of Health and Human Services (HHS), provided Moderna with approximately $1.4 billion for nonclinical and clinical research to

[12] Anthony E. Kiszewski, Ekaterina Galkina Cleary, and Matthew J. Jackson, et al., "NIH Funding for Vaccine Readiness Before the COVID-19 Pandemic," *Vaccine*, vol. 39 (2021), pp. 2458-2466.

[13] CRS calculations based on DARPA budget documents. The $400 million figure represents the total amount for the ADEPT and P3 programs, of which an unspecified portion went to non-mRNA related development.

[14] DARPA, "Autonomous Diagnostics to Enable Prevention and Therapeutics (ADEPT)," https://www.darpa.mil/program/autonomous-diagnostics-to-enable-prevention-and-therapeutics.

[15] DARPA, "COVID-19," https://www.darpa.mil/work-with-us/covid-19.

[16] DARPA, "Pandemic Prevention Platform (P3)," https://www.darpa.mil/program/pandemic-prevention-platform.

develop an mRNA COVID-19 vaccine and to expand manufacturing facilities through Operation Warp Speed.[17]

Market Projections and Private Investment

A few market research firms have published market projections for mRNA-based vaccines and therapeutics. Although estimates vary widely due to different underlying assumptions, these firms generally predict robust growth for the mRNA vaccine and therapeutic global market.

- In August 2020, India-based IMARC estimated that the global market for mRNA vaccines and therapeutics would grow at a compound annual growth rate (CAGR) of 10.5%, from $9.41 billion in 2021 to $15.49 billion in 2026.[18]
- In October 2021, Ireland-based Research and Markets estimated that the global market for mRNA therapeutics would increase from $46.7 billion in 2021 to $101.3 billion in 2026, a CAGR of 16.8%.[19]
- In 2021, U.S.-based BIS Research estimated that the global market for COVID-19 mRNA vaccines and therapeutics would decrease from $51.65 billion in 2021 to $28.92 billion in 2025, a CAGR of -13.5%. However, for non-COVID-19 mRNA vaccines and therapeutics, BIS Research estimated that the global market would increase from $0.05 billion in 2026 to $1.69 billion in 2031, a CAGR of 95.5%.[20]

Private investments are a commonly used metric for assessing the economic potential of a technology. Investments are being made by and in companies of varying size and technology maturity that are conducting mRNA R&D. In addition to numerous mergers and acquisitions, these companies are engaging in a wide range of collaborations and partnerships. Below are several examples of investments in, acquisitions of, and partnerships with mRNA technology firms:

- Sanofi, a biopharmaceutical company headquartered in Paris, France, acquired Bio Translate, a clinical-stage mRNA therapeutics company based in Lexington, MA, for $3.2 billion in August 2021.[21]
- AbCellara, a biotech company headquartered in Vancouver, Canada, and Moderna, an mRNA vaccine and therapeutics company headquartered in Cambridge, MA, announced a multi-year research collaboration in September

[17] CRS calculations based on public award announcements. See "BARDA's Expanding COVID-19 Medical Countermeasure Portfolio," at https://www.medicalcountermeasures.gov/app/barda/coronavirus/COVID19.aspx. Pfizer/BioNTech, the other successful mRNA vaccine developer, did not receive U.S. government funds to conduct R&D.

[18] IMARC, "Global mRNA Vaccines and Therapeutics Market to Reach US$ 15.49 Billion by 2026, Spurred by Increasing Investments in Biotechnology," August 31, 2020, https://www.imarcgroup.com/global-mrna-vaccines-therapeutics-market.

[19] Research and Markets, "Outlook on the mRNA Global Market and Therapeutics to 2026," October 6, 2021, https://www.globenewswire.com/news-release/2021/10/06/2309400/28124/en/Outlook-on-the-mRNA-Global-Market-and-Therapeutics-to-2026.html.

[20] BIS Research, "Global mRNA Vaccines and Therapeutics Market," 2021, https://bisresearch.com/industry-report/mrna-vaccines-therapeutics-market.html.

[21] Sanofi, "Sanofi to Acquire Translate Bio; Advances Deployment of mRNA Technology Across Vaccines and Therapeutics Development," August 31, 2021, https://www.sanofi.com/en/media-room/press-releases/2021/2021-08-03-07-00-00-2273307.

2021 that will use "AbCellera's AI-powered technology to search and analyze natural immune responses to identify therapeutic antibodies against up to six targets selected by Moderna."[22]

- Strand Therapeutics, an mRNA therapeutics startup based in Cambridge, MA, raised $52 million in June 2021 to advance the development of its mRNA platform for cancer immunotherapies and enter into clinical trials.[23]
- Abogen Biosciences, a China-based biotech company, raised over $700 million in August 2021 to support clinical trials on its mRNA-based COVID-19 vaccine and the development of other mRNA-based vaccines and treatments.[24]

Potential Considerations for Congress

The following sections address selected areas that Congress might consider in determining whether and how to support the advancement of mRNA technologies.

Role of the Federal Government

There is general agreement that the federal government's role in supporting basic research and the creation of foundational knowledge was important for the subsequent development of mRNA technologies. Some experts have noted, however, that in response to the COVID-19 pandemic the federal government shifted its support to activities generally left to the private sector, including late-stage clinical trials and research, product development, and manufacturing.[25] This shift has caused some to raise a number of questions about what, if any, changes may be appropriate regarding federal support for biomedical research and innovation, including advancements in mRNA technologies, beyond the context of the COVID-19 pandemic. The appropriate role of the federal government in late-stage R&D is not a new issue; however, the pandemic would mark an inflection point if Congress were to continue increased support for such activities.

Beyond the degree to which the federal government should provide late-stage research and innovation funding for mRNA and other biomedical technologies, questions have been raised regarding traditional funding mechanisms. For example, a number of articles have been written about how Dr. Katalin Karikó—whose pioneering work on mRNA helped form the foundation for the mRNA-based COVID-19 vaccines—was unable to get her research funded by NIH.[26] NIH

[22] AbCellera, "AbCellera Announces Collaboration with Moderna to Discover Therapeutic Antibodies for mRNA Medicines," September 15, 2021, https://www.abcellera.com/news/abcellera-collaboration-moderna.

[23] Strand Therapeutics, "Strand Therapeutics Raises $52M in Oversubscribed Series A Round," June 23, 2021, https://www.businesswire.com/news/home/20210623005302/en/Strand-Therapeutics-Raises-52M-in-Oversubscribed-Series-A-Round.

[24] Nick Paul Taylor, "China's Abogen Raises $700M Series C for mRNA Trials, Catapulting Itself into the Big Leagues," August 20, 2021, https://www.fiercebiotech.com/biotech/china-s-abogen-raises-700m-series-c-for-mrna-trials-catapulting-itself-into-big-leagues.

[25] Bhaven N. Sampat and Kenneth C. Shadlen, "The COVID-19 Innovation System," *Health Affairs*, vol. 40, no. 3 (February 4, 2021), https://www.healthaffairs.org/doi/full/10.1377/hlthaff.2020.02097#B21.

[26] See, for example, Damian Garde and Jonathan Saltzman, "The Story of mRNA: How a Once-Dismissed Idea Became a Leading Technology in the COVID Vaccine Race," *STATNews*, November 10, 2020, https://www.statnews.com/2020/11/10/the-story-of-mrna-how-a-once-dismissed-idea-became-a-leading-technology-in-the-covid-vaccine-race/; and Carolyn Y. Johnson, "Vaccine Vanguard: A One-Way Ticket. A Cash-Stuffed Teddy Bear. A Dream Decades in the Making," *Washington Post*, October 1, 2021, https://www.washingtonpost.com/health/2021/10/01/katalin-kariko-covid-vaccines/.

funds most of its research through the scientific peer review process—a committee-based review process to evaluate scientific, investigator-driven research proposals for funding.[27] Some analysts suggest that this investigator-driven and consensus-based process may not adequately fund "high-risk, high-reward" projects,[28] a term often associated with projects that have high potential for meeting fundamental scientific or technological challenges and that involve a high degree of novelty and/or multidisciplinary approaches.[29] Support for high-risk, high-reward research is widely considered an important element in developing breakthrough technologies that address societal challenges, including health-related challenges, and in maintaining the economic competitiveness of the United States.[30]

Through FY2022 appropriations, Congress provided $1 billion to HHS to establish the Advanced Research Projects Agency for Health (ARPA-H).[31] Some view ARPA-H as a necessary response to concerns about the risk aversion of traditional funding mechanisms, as well as a way to accelerate the development of biomedical technologies.[32] According to a concept paper issued by the Biden Administration, one of the potential projects that ARPA-H could pursue is the development of mRNA-based vaccines that would prevent most cancers.[33] President Biden's FY2023 budget request proposes $5 billion for ARPA-H in an NIH account, with funding available until September 30, 2025.[34] Congress could consider how to define the mission of ARPA-H and the activities it would support, in addition to providing funding for the agency, if it seeks to use this approach to advance the development of mRNA technologies.

Coordination of Federal Research

According to an Organization for Economic Cooperation and Development (OECD) workshop, *Priority Setting and Coordination of Research Agendas: Lessons Learned from COVID 19*:

> Priority setting, steering and coordination of research efforts has been a major challenge. From the policy perspective, different parts of government have different priorities and different requirements for scientific evidence and research. In the absence of effective

[27] See "Peer Review Process for Extramural Funding" in CRS Report R41705, *The National Institutes of Health (NIH): Background and Congressional Issues*, by Judith A. Johnson and Kavya Sekar.

[28] Chiara Franzoni, Paula Stephan, and Reinhilde Veugelers, "Funding Risky Research," *National Bureau of Economic Research Working Paper*, June 2021; Mikko Packalen and Jay Bhattacharya, "NIH Funding and the Pursuit of Edge Science," *Proceedings of the National Academy of Sciences*, vol. 117, no. 22 (June 2, 2020), pp. 12011-12016; and Pierre Azoulay, Erica Fuchs, and Anna Goldstein, "Funding Breakthrough Research: Promises and Challenges of the 'ARPA Model,'" *National Bureau of Economic Research*, June 2018.

[29] For a discussion of definitions of "high-risk, high-reward research," see pp. 11-13 of Organization for Economic Cooperation and Development (OECD), *Effective Policies to Foster High-Risk/High-Reward Research*, OECD Science, Technology, and Industry Policy Papers, No. 112, May 2021, https://read.oecd.org/10.1787/06913b3b-en?format=pdf.

[30] Organization for Economic Cooperation and Development (OECD), *Effective Policies to Foster High-Risk/High-Reward Research*, OECD Science, Technology, and Industry Policy Papers, No. 112, May 2021, https://read.oecd.org/10.1787/06913b3b-en?format=pdf.

[31] For more on ARPA-H see, CRS Report R47074, *Advanced Research Projects Agency for Health (ARPA-H): Congressional Action and Selected Policy Issues*, by Kavya Sekar and Marcy E. Gallo.

[32] For example, see Suzanne Wright Foundation, "HARPA: Health Advanced Research Projects Agency," https://www.harpa.org/; and Bhaven N. Sampat and Robert Cook-Deegan, "An ARPA for Health Research?," *Milbank Quarterly*, https://www.milbank.org/quarterly/opinions/an-arpa-for-health-research/.

[33] White House, *Advanced Research Project Agency for Health (ARPA-H): Concept Paper*, https://www.whitehouse.gov/wp-content/uploads/2021/06/ARPA-H-Concept-Paper.pdf.

[34] NIH, *Congressional Justification: FY2023*, March 28, 2022, p. 33, https://officeofbudget.od.nih.gov/pdfs/FY23/br/Overview%20of%20FY%202023%20Presidents%20Budget.pdf.

> cross-government (and cross-agency) coordination, this can lead to fragmentation and/or duplication of research efforts, with insufficient attention being given to some areas (such as PHSMs [public health and social measures]).[35]

Advancement of mRNA technologies, including the development of mRNA-based vaccines in response to future pandemics, might benefit from the development of a research roadmap, a federal standing committee, or a process for coordination and communication. In 2020, NIH created the "Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) public-private partnership to develop a coordinated research strategy for prioritizing and speeding development of the most promising [COVID-19] treatments and vaccines."[36] ACTIV is coordinated by the Foundation for the National Institutes of Health and includes NIH, BARDA, FDA, the Centers for Disease Control and Prevention, the Department of Defense, the Department of Veterans Affairs, the European Medicines Agency, and representatives from academia, philanthropic organizations, and biopharmaceutical companies.[37] Congress could consider modifying ACTIV or creating a similar mechanism for post-COVID-19 research coordination. An assessment by the Office of Science and Technology Policy, the Government Accountability Office, or the National Academies of Science, Engineering, and Medicine might also be helpful in suggesting strategies for increased and enhanced coordination of mRNA R&D.

After past disease outbreaks, such as Ebola and Zika, federal funding for related research declined. A similar decline in research funding for mRNA technologies after the COVID-19 pandemic subsides, some argue, might stunt the projected growth in this field. Continued and enhanced cross-agency coordination and evaluation of federal R&D efforts associated with mRNA technologies and their potential in future pandemics might also help to address such concerns.

U.S. Competitiveness

While the United States remains the global leader in the life sciences, concerns about future leadership abound. According to the Information Technology and Innovation Foundation,

> During the last few decades, other nations have come to realize the importance of the [life sciences] sector to their economies and have therefore increasingly tried to win a larger share of global life-sciences activity. These efforts have been marginally successful, in part because U.S. policy has been less than fully adequate. The competitive threat is important because if the United States' advantage of having a strong ecosystem gets eroded beyond a certain point, it will be extremely difficult to regain.[38]

As indicated above, many expect mRNA technologies to play a prominent role in the future of the pharmaceutical industry and medicine. If the United States seeks to maintain its leadership role in the life sciences broadly, and in mRNA technologies, specifically, then Congress may consider options to ensure the implementation of robust federal policies, which may include increased

[35] OECD Global Science Forum, Workshop on "Priority Setting and Coordination of Research Agendas: Lessons Learned from COVID-19," Workshop Summary, January 20, 2022, https://one.oecd.org/document/DSTI/STP/GSF(2021)21/FINAL/en/pdf.

[36] NIH, "Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)," https://www.nih.gov/research-training/medical-research-initiatives/activ.

[37] Foundation for the National Institutes of Health, "About ACTIV," https://www.fnih.org/our-programs/activ/about.

[38] Joe Kennedy, *How to Ensure That America's Life-Sciences Sector Remains Globally Competitive*, Information Technology and Innovation Foundation, Washington, DC, March 2018 (Revised July 2020), p. 1, https://www2.itif.org/2018-life-sciences-globally-competitive.pdf.

federal R&D funding; an effective regulatory environment; a well-trained and adequate life sciences workforce; and public and private sector coordination.

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