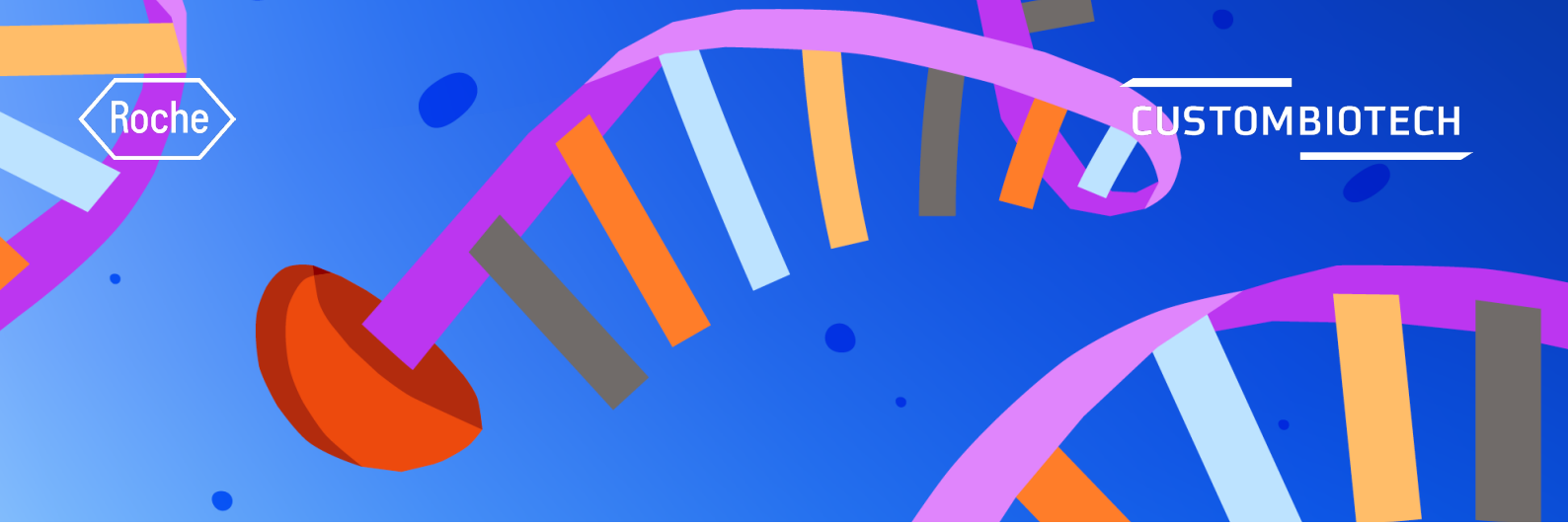


# The future of mRNA: four key focuses for industry

2024

In the wake of the pandemic, mRNA-based therapeutics and vaccines have seen increasing research and development interest, owing to their potential to address a wide range of therapeutic indications, from infectious diseases to genetic disorders to cancer. There exists promising versatility within mRNA technology: for example, for targets such as intracellular proteins that are inaccessible to many protein-based therapeutics, mRNA drugs can be leveraged to induce therapeutic effects. Moreover, the speed with which mRNA drugs can be developed without sacrificing quality means these assets are poised to represent an increasingly large segment of the biotherapeutic development pipeline in the coming years.[1,2]

In contrast to recombinant protein therapies, which are typically dependent on secreted proteins, mRNA can be encoded with transmembrane proteins or supplemented with intracellular proteins to address targets not accessible to recombinant proteins. These applications possess unique pharmacokinetic profiles, working transiently and exhibiting steep peaks and abrupt disappearance, mimicking many of the body's own biological functions and thereby enabling a broader range of theoretical purposes and novel targets.

As developers explore the potential applications for mRNA alongside the delivery mechanisms best suited to maximizing their therapeutic potential, these drugs are likely to experience even more interest in the research and clinical spaces. With efforts aimed at refining purification, improving both mRNA and carrier system stability, and simplifying storage and transport requirements, the industry is likely to see breakthroughs that position mRNA as a major player in the broader advanced therapy space.

## Targets for mRNA innovation

The demand for new and innovative therapies, particularly those that can treat previously undruggable targets, has galvanized increased investigations into the potential of mRNA drugs. When it comes to achieving scale for mRNA products, there are a number of key considerations for industry, including:

**Optimizing purification:** Developing more scalable chromatography columns is among the major challenges for the mRNA space today. Often, large-scale production using these systems results in diminishing returns on yields. As such, planning early in the near-term can help developers more effectively plan for the facility requirements that accompany large-dose applications. Additionally, many have begun exploring column-free alternatives for mRNA purification, though this often engenders longer development timelines and more stringent risk assessment.

**Improving carrier systems:** The majority of RNAs in development today are delivered using lipid nanoparticles (LNPs), which, while well-characterized in some respects, still require significant R&D to understand all the variables influencing their safety. Many LNP formulations tend to aggregate[3] under the wrong conditions, rendering them potentially injurious to human health or less efficacious, as mRNA is prematurely released. As such, finding ways to exclude these aggregates, better understand the influence of LNP size on immunogenicity, and better stabilize suspension for these payload vehicles is crucial.

**Simplifying storage by improving stability:** There exists significant opportunity to improve stability for mRNA drugs, enabling them to be stored at more standard temperature ranges than those needed for the first COVID-19 vaccines. There are aspects of LNPs that support the potential for lower temperature requirements, and many have been demonstrated to remain stable at much warmer temperatures than the -80 C° that was typical of the first mRNA COVID vaccines.[4] For respiratory diseases, emerging formulation approaches employing lyophilization could result in more stable formulations. [5] [6]

**Managing supply chain constraints:** Supply chain constraints remain a key consideration for biopharmaceutical development even after the most disruptive months of the pandemic have passed. Addressing the problem requires organizations to remain aware of their own timelines as well as those impacting the wider industry. Derisking supply chain starts with finding the right partners and communicating with those partners clearly and frequently. The bottlenecks seen during the pandemic have caused the CDMO industry to expand significantly, so that organizations have access to more third-party capacity and expertise than ever before.

## Looking toward the future

The goals for the mRNA industry, ultimately, are scalable processes that do not compromise quality and can produce safe, efficacious drugs that can be transported and stored at refrigeration temperatures. With efforts aimed at refining purification for these drugs and improving both mRNA and carrier system stability, the industry is likely to see breakthroughs in scalability, potency, and stability for these modalities. In the face of both regulatory and technical uncertainty, mRNA developers must engage in proactive innovation across every phase of the development lifecycle, from better manufacturability assessments to optimized downstream processing, in order to arrive at a well-defined and high-quality manufacturing process.

Roche CustomBiotech is renowned for delivering high-quality raw materials and solutions that meet stringent industry requirement.

**About Roche CustomBiotech**

From vaccines and immunotherapies to protein replacement and cell reprogramming, interest in mRNA manufacturing has surged. Decades before the pandemic, Roche CustomBiotech has supplied nucleotides and enzymes for mRNA production. We work with many pioneering mRNA companies to develop and manufacture needed raw material solutions. In collaboration with therapeutic manufacturers, our portfolio has evolved to meet the changing needs of the mRNA field. Always abreast with market developments, Roche CustomBiotech enables a new generation of mRNA therapeutics. Our guiding tenet is to minimize variation of products built on our raw materials by ensuring best quality, high performance within narrow tolerances, and reliable delivery.


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**Please contact your local CustomBiotech representative**


**Europe, Middle East, Africa, Latin America**
mannheim.custombiotech@roche.com

**United States**
custombiotech.ussales@roche.com

**Canada**
custombiotech.can@roche.com

**Asia Pacific**
apac.custombiotech@roche.com