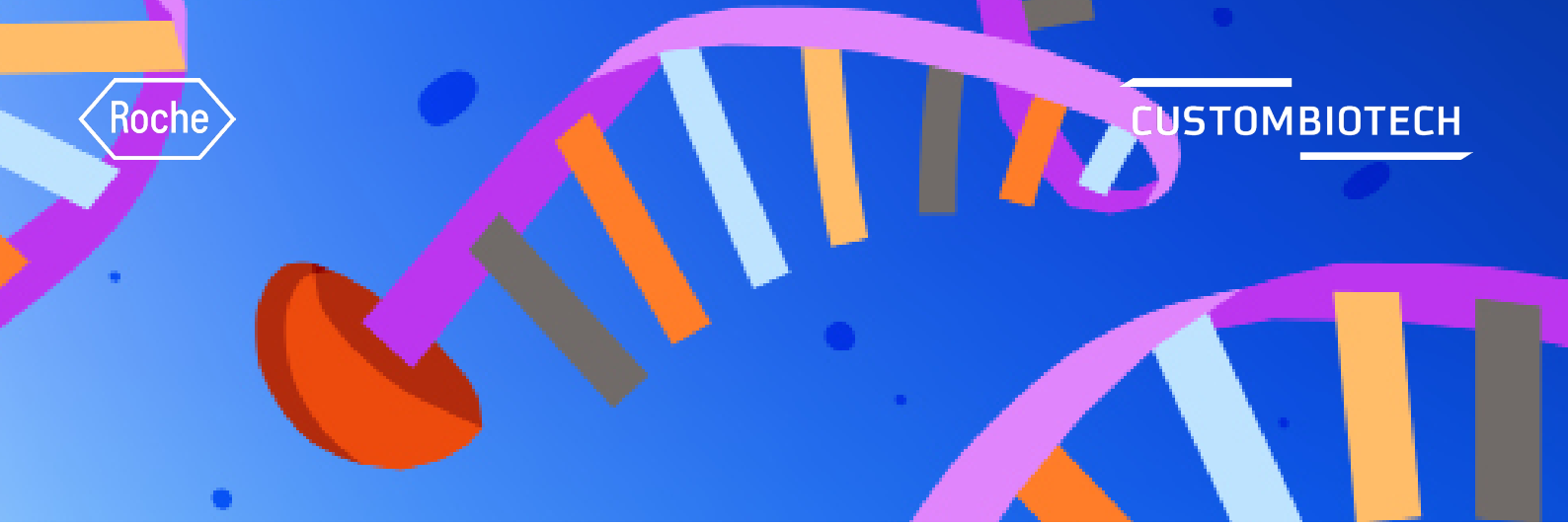

Reducing risk in mRNA therapeutic development

2024

The high demand for new and more efficacious therapies, particularly for previously undruggable targets, has resulted in increased focus on mRNA-based therapies. These drugs, which have seen increasing research and development interest in the wake of the pandemic, have the 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 targets such as intracellular proteins, which are inaccessible to many protein-based therapeutics, mRNA drugs can be leveraged to induce therapeutic effects. Likewise, the speed with which mRNA drugs can be developed without sacrificing quality means that these assets are poised to represent an increasingly large segment of the biotherapeutic development pipeline in the coming years.

mRNA can principally encode almost any protein; in contrast to recombinant protein technologies, 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.[1,2] These modalities possess unique pharmacokinetic profiles, working transiently and exhibiting steep peaks and abrupt disappearance.[3] This activity mimics many of the body's own biological functions, enabling a broader range of theoretical purposes and driving more novel targets. The potential for these drugs, both in the face of intractable diseases and evolving cost pressures, make addressing supply chain constraints and remaining technical challenges paramount to ensuring their wider success.

In the mRNA therapeutic and vaccine space, there are a number of rate-limiting factors that introduce the potential for delays in development and commercialization. From purification scalability to safety profiles, carrier system stability to supply chain, the factors that create complexity for these modalities represent formidable challenges for the industry.

Achieving safer, more scalable mRNA drugs

When it comes to achieving scale for mRNA products, establishing efficient, reliable purification strategies that minimize impurities requires a focus on achieving scalable chromatography systems. Scaling chromatography columns is a time-intensive and complex endeavor, as achieving large-scale production (40-70 liters) with these systems often comes at the expense of yields. For applications where large volumes of drug substance must be produced, as in the case of COVID-19 vaccines, planning early for this eventual scale can help developers incorporate more versatility into a process. Alternative technologies and methods have begun to emerge to enable column-free purification for mRNA, particularly those that leverage tangential flow filtration (TFF), but each comes with the promise of longer development timelines and a considerable amount of risk assessment. The impurity profile of a product is likely to change with any transition in technology, but emerging solutions using technologies like TFF are gaining traction for their scalability.

A key consideration for development and scale-up for these therapeutics is the type of RNA being leveraged. Self-amplifying mRNA, for example, exhibits prolonged expression in comparison to many other forms of RNA, but its size creates additional complexity for production and stability, and non-structural proteins generated during production could increase immunogenicity in gene therapy applications. Ultimately, linear mRNA is the most well-understood of the various RNA technologies, while others like circular mRNA are experiencing increasing development interest owing to their potential for certain applications, but still lack the same degree of characterization.

The goal for industry, ultimately, is a scalable process that does not compromise quality. The safety profile of mRNA vaccines has been well demonstrated in recent years. There exists, comparatively, much less data for mRNA-based therapeutics, but their own safety profiles and propensity for inducing immune response are likely to tie directly to the level of purity operators are able to achieve for these products. As more data is generated in human studies, researchers and operators will uncover the fundamental drivers behind side effects and immunogenicity for mRNA-based therapies. mRNA is fairly unstable, particularly prior to being complexed into a delivery system such as a lipid nanoparticle (LNP). In order to protect mRNA from degradation, most operations require stringent sterility protocols. The risk of carryover is low for these products, which are amenable to single-use systems in their manufacturing, further minimizing risk.

Lipid nanoparticle delivery: improving the package

The majority of RNAs are delivered using LNPs, most of which are comprised of similar components – an ionizable cationic lipid, cholesterol, a polyethylene glycol-lipid, and a phospholipid, each of which drives the LNP's efficacy or stability. One of the major challenges inherent in LNP production is the stability of LNP suspensions. Many LNP formulations have a tendency to aggregate under the wrong conditions, meaning they either form agglomerations potentially injurious to human health or suffer from integrity losses as mRNA is prematurely released. Achieving size exclusion for these aggregations in order to stabilize suspension can serve to significantly improve an mRNA-LNP's safety profile; likewise, selecting the best component parts for an LNP is crucial to minimizing undesired side effects for these drugs.

While some of the variables influencing immunogenicity and safety for LNPs are understood, others are not. Currently, most LNPs leveraged for these modalities are between 60 to 100 nanometers in size. Data on size as a contributor to immune stimulation is so far inconclusive; moreover, there are difficulties in generating LNPs in distinct size variations for the purpose of testing, as this has a tendency to change other parameters for the particle.

Managing supply chain and improving stability to enable more mRNA

Supply chain constraints remain a key consideration for biopharmaceutical development even after the most disruptive months of the pandemic have passed. Lead times for a sterile filter may be upwards of six months, even today; to address issues like this 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.

The accelerated pace at which mRNA vaccines were developed and produced in response to the pandemic, while both necessary and impressive, has meant that there exists significant opportunity to improve stability for these drugs to enable them to be stored at more standard temperature ranges. This applies to mRNA-based therapeutics as well – ideally, the industry can reach a point where these modalities can be stored at temperatures that would allow them to be kept in a patient's home. 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. For respiratory diseases, differing formulation approaches such as dried powders could result in more stable formulations.[4]

Ultimately, as developers explore the future of the various types of 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 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. Additional efforts around lyophilizing these drugs or otherwise simplifying their storage and transport requirements are poised to represent a sea change for industry.

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.

References

1 Niazi SK, Magoola M. mRNA and Synthesis-Based Therapeutic Proteins: A Non-Recombinant Affordable Option. Biologics. 2023; 3(4):355-379. https://doi.org/10.3390/biologics3040020.
2 Qiongyu Duan et al. How far are the new wave of mRNA drugs from us? mRNA product current perspective and future development. Frontiers in Immunology. 2022; Volume 13. https://doi.org/10.3389/fimmu.2022.974433.
3 Molin C, Jauhiainen A, Warringer J, Nerman O, Sunnerhagen P. mRNA stability changes precede changes in steady-state mRNA amounts during hyperosmotic stress. RNA. 2009 Apr;15(4):600-14. doi: 10.1261/rna.1403509. Epub 2009 Feb 17. PMID: 19223440; PMCID: PMC2661839.
4 Challener, Cynthia A. Increasing mRNA Product Stability with Lyophilization. BioPharm International. 2024, Volume 37, Issue 2, Pages: 22-25.

Published by
Roche Diagnostics GmbH
Sandhofer Str. 116
68305 Mannheim
Germany

custombiotech.roche.com

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