The Next Wave of RNA Therapeutics

What comes after the success of SARS-CoV-2 mRNA vaccines? We explore the potential of self-amplifying RNA and circular RNA in the future of drug development.

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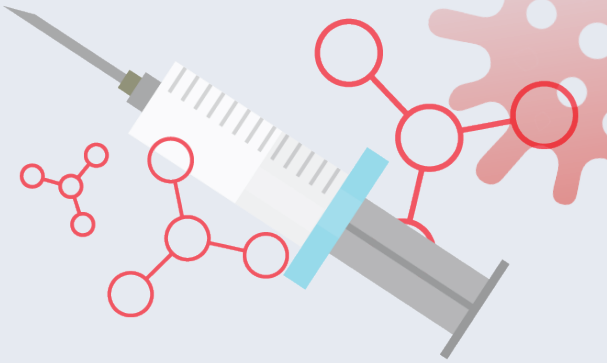
SARS-CoV-2 is not the first viral crisis the world has faced, and it will not be the last—a stark reminder that we must invest in technologies that can help develop effective vaccines quickly and safely. We have all come to realize that mRNA is a powerful therapeutic modality; mRNA vaccines were rapidly designed, developed, manufactured, and approved to counter the rising threat—and, for the most part, they have been accepted by patients. Following mRNA's newfound success, pharmaceutical stakeholders are keen to delve into applications beyond SARS-CoV-2. Vaccines against other infectious diseases and enhanced personalized medicines for cancer are both possibilities using an mRNA-based approach.

Unlike traditional (protein-based) biopharmaceuticals, the mRNA manufacturing process is cell-free, making it simpler. However, to move forward, the industry must improve its collective understanding of mRNA. Manufacturers are still tackling the twin issues of quality and stability—the reason why mRNA-based products require ultra-low storage temperatures, which limits how and where they can be used. Equally concerning is the lack of clear and thorough regulatory guidance; there are no well-defined acceptance criteria for mRNA therapeutics. Yes, regulators were supportive of companies' vaccine development programs throughout the coronavirus crisis, but there is still far to go before robust guidelines are established for the development of therapeutics beyond SARS-CoV-2. For example, knowledge around impurity profiles and critical quality attributes must be enhanced so that companies can improve their understanding of what can be accepted and released as a final drug or vaccine.

As well as improving upon traditional mRNA, investment is also being directed to other RNA formats, particularly self-amplifying (saRNA) and circular RNA (circRNA). The unique structures of saRNA and circRNA mean that smaller doses—almost 10 times less—can be administered to patients. An additional benefit? Once administered, the expression of these molecules can last for a longer period. Therefore, companies can expect to save costs by manufacturing lower volumes, while also reducing the dose burden for patients. Lower doses could also translate to fewer potential side effects.

Therapies of the future

There are several key differences in molecular structure between traditional mRNA, saRNA, and circRNA. Traditional mRNA has a linear form that includes a poly(A) tail and cap. As the name suggests, saRNA can replicate, using molecular machinery that is not present in traditional mRNA molecules. It still has a poly(A) tail and cap, but the overall size of the RNA is larger than traditional mRNA (the additional sequence is required to drive self-amplification). circRNA is a closed-loop structure formed from a single strand; as such, it has no poly(A) tail or cap. Importantly, the closed-loop structure offers protection from exonuclease degradation, improving the stability of circRNA, which is very compelling from a drug development point of view.



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A Truly Exciting Modality

Why is RNA technology so compelling?

For Pirkko Muhonen, nucleic acid–based therapeutics have always been an exciting topic. "mRNA and the mRNA production workflow has been an interest of mine, even before I joined the Nucleic Acid Therapeutics team at Thermo Fisher Scientific earlier this year. When SARS-CoV-2 hit and conversations about mRNA vaccine manufacturing really took off, my colleagues and I were able to seize the opportunity to take part in this important and exciting technology development. It's incredible to see how the field has evolved in such a short space of time."

For Sirat Sikka, RNA was an intriguing topic long before SARS-CoV-2. "It was easy to synthesize and purify. It took less than a week to generate RNA expressing the target protein. It was fascinating. The significant therapeutic potential was evident, and a simple rapid process was an advantage. There is still so much to discover. In time, there may be other formats and formulations that could help us find new and better ways of tackling vaccines for various diseases, gene editing, diagnosis, and targeting cardiovascular and central nervous system diseases. It's a very exciting time."

translated in cells. These structural differences result in processing differences. For instance, as circRNA does not have a poly(A) tail or cap, synthesis is more streamlined, but this can present challenges downstream because you cannot use a purification method that relies on capturing by the poly(A) tail. Therefore, different purification approaches will be required for circRNA. saRNA is significantly larger than traditional mRNA molecules, which leads to challenges during production, such as increased product-related impurities during synthesis and lower binding capacities in chromatography steps due to its larger size. We must consider how we can improve the overall process—after all, the level of impurities and ability of a molecule to bind within a column directly affects production costs and time, as well as the manufacturing footprint.

Perhaps an even more complex challenge facing saRNA- and circRNA-based therapeutics is the inability to use modified nucleotides, upon which today's approved mRNA vaccines rely on to minimize immunogenicity. Ongoing research is exploring this complex issue—another balancing act between immunogenicity and efficacy.

Time to prioritize

Process development and manufacturing challenges continue to be investigated with fervor. Calls for improved regulatory guidance, particularly when it comes to analytical method development, will undoubtedly continue and increase in volume. At the same time, process improvements and optimization to increase yield and drive costs down are just getting started.

SARS-CoV-2 has accelerated the acceptance of mRNA in vaccines, and the amount of new investment entering the field gives drug developers an unprecedented opportunity to explore the modality and dig into how the different formats can be best used to target different diseases—not only as therapeutics, but potentially as diagnostics as well. saRNA and circRNA may not necessarily replace traditional mRNA formats, but they do represent new approaches with certain benefits, including lower costs.

At Thermo Fisher Scientific, we recognize RNA as an important modality for the future. We are investing heavily to develop products and solutions to help customers boost their understanding of the modality, while also working on streamlining and simplifying processes to lower production costs. We are in constant communication with customers working on RNA technologies, and we are learning alongside them to innovate and deliver solutions and services that help with all aspects of RNA manufacturing, including synthesis, purification, and formulation.