mRNA: A New Frontier in Vaccines and Medicine

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Overview

Vaccines have revolutionized the world's ability to prevent, mitigate the impact of and, in some cases, eliminate the threat of certain infectious diseases and improve overall health. The clinical development of a conventional vaccine is a complex and lengthy process involving rigorous safety and efficacy testing that can take 10-15 years to complete.

Prior to the COVID-19 pandemic, the mumps vaccine was the fastest vaccine developed — going from viral sampling to licensure — in four years. The global COVID-19 pandemic, occurring six decades later, provided an acute need to accelerate vaccine development to previously unimaginable speeds – less than one year from sequencing of the viral genome to emergency use authorization. This achievement has forever changed the landscape of vaccine development and brings with it hope that vaccines for other pathogens can be developed on an accelerated timeline.

The emergence of the SARS-CoV-2 virus and the resulting COVID-19 global health crisis highlighted the need for vaccines that could safely protect from severe disease while reducing infection rates in vaccinated populations, eliciting long-term memory immune responses and offering the potential for rapid and cost-effective manufacturing in extremely large quantities, all while providing global accessibility. To answer this unmet need, messenger ribonucleic acid (mRNA) vaccines quickly surged to the forefront of COVID-19 vaccine candidates.

Potent inducers of both cellular and humoral adaptive immune responses, mRNA vaccines are very fast to deploy and, because of the quick degradation of nucleic acid within the body, were expected to have a favorable safety profile. Further, since the primary ingredient required for production is the genetic sequence that encodes for a viral antigen, design and production could be fast-tracked. Less than 10 weeks after the first genetic sequences were released, one prominent biotech company's mRNA-based SARS-CoV-2 vaccine candidate entered Phase I trials.

Although mRNA technology has been in development for more than 30 years, it was the current pandemic that spurred the translation of the largely theoretical benefits of mRNA technology into the current reality of mRNA-based vaccines that have likely saved millions of lives. In this article, we will provide an overview of this promising technology platform in the new era of vaccine and therapeutic drug development.

Introduction to Nucleic Acid Vaccines

Conventional vaccines require an antigen to be injected into the body to induce an immune response in the host. In contrast, mRNA vaccines use a piece of ribonucleic acid that corresponds to a viral protein to direct cells to produce copies of that viral protein, which triggers an immune response. Since recipients are not exposed to the actual live virus in mRNA vaccines, they cannot become infected through vaccination.

This innovative platform represents a promising alternative to conventional approaches in vaccine research and development, as well as potential revolutionary breakthroughs in therapeutic medicine. Currently, there are several investigational mRNA-based vaccine candidates in early-stage clinical development that target various indications and therapeutic areas, including both preventative and therapeutic settings.

Advantages and Disadvantages of mRNA Vaccines

One of the greatest advantages of mRNA over conventional vaccines is the relatively simple manufacturing process that can rapidly be scaled to respond to epidemics. The mRNA backbone of these vaccines remains constant – only the coding region of the vaccine is changed to address different indications. Once the genetic sequence of a virus is understood, the coding region of the mRNA backbone can be rapidly adjusted to encode for the new pathogen. This process accelerates research and development along with a faster response to novel threats and efficient, large-scale standardized production. In addition, production is based on an in vitro cell-free transcription reaction, which minimizes the risk of cell-derived impurities and viral contaminants that are often found in other vaccine platforms.1

Another advantage is the ability to mimic various aspects of a natural viral infection once it enters the cells. Upon cell entry, mRNA produces viral antigen proteins from within the cells that include natural, post-translational modifications that imitate the occurrence of a natural viral infection. These endogenously produced viral proteins elicit an enhanced immune response, including stronger B- and T-cell responses than are seen with traditional protein subunit vaccines.2 Additionally, multiple mRNAs encoding for multiple viral proteins can be included in a single vaccine, permitting the production of complex multimeric antigens.

Cost and sustainability of the manufacturing process are the two leading downsides to the use of this technology. Today, the materials required for the in vitro transcription enzymatic reaction used to generate mRNA are expensive and limited. Further, downstream processing of the vaccine – including mRNA purification steps – remains difficult to scale and is costly.3 The use of new production methods such as continuous manufacturing, the reuse of scarce/high-cost ingredients/compounds and high-throughput purification methods should mitigate most of these concerns in the future.

The storage of mRNA drug products also remains a concern. There is little published data on the stability and storage of formulated mRNA drug product stability (i.e., LNP-mRNA and protein-mRNA complexes).4 For example, the current stability profile of authorized and approved COVID-19 vaccines requires cold-chain storage, ranging from around -70 degrees Celsius to -20 degrees Celsius during shipping, and from 2 degrees Celsius to 8 degrees Celsius when diluted for administration. This is a clear competitive disadvantage in the marketplace and limits the viability of these vaccines in many regions of the world. Future generations of mRNA vaccines will need to incorporate changes in formulation and manufacturing processes to move away from freezing conditions for long-term storage.

mRNA Vaccine Safety

The safety of vaccine recipients is paramount, and as such remains the top priority for the development of any vaccine.5 Even after a vaccine is licensed and recommended for use, health agencies require collection and monitoring of real-world data (RWD) on safety and effectiveness across a wide variety of people with diverse characteristics including age, ethnic background, gender and underlying medical conditions.

Worldwide, cross-pharma and public-private partnerships and collaborations have been launched to monitor for SARS-CoV-2 variants of concern and to help answer questions relating to long-term, brand-specific COVID-19 vaccine safety and effectiveness.6 This includes the duration of protection and the benefit of additional vaccine doses, as well as their interchangeability in real-life settings. For health authorities to provide guidance and recommendations about risks and benefits of COVID-19 vaccination, this scientific information is essential.

In general, mRNA vaccine technology combines the advantages of live-attenuated vaccines, such as endogenous antigen expression and T-cell induction, with the outstanding safety profile of inactivated or protein subunit vaccines. It promotes both humoral and cellular immune response and induces the innate immune system.

Unlike attenuated or inactivated vaccines, mRNA is precise. It only will express a specific antigen and induce a directed immune response. Additionally, expression of the coded antigens is transient since mRNA is quickly degraded by cellular processes, with no traces found after two to three days. As a result, the risk of random genome integration is virtually zero, unlike the theoretical risk of DNA vaccines.

Future Trends in mRNA Technology

The success of mRNA vaccines provides the potential to launch a second "Golden Age of Medicine." Given its expedited manufacturing properties and "plug and play" platform structure, mRNA technology likely will become the mainstay of epidemic and pandemic rapid response in both the vaccine and therapeutic medicine realms.

The ability of the mRNA vaccine backbone to be conserved while swapping out the mRNA sequence that codes one pathogenic protein for another means that multicomponent vaccines targeting several different strains within one virus family — and universal vaccines targeting multiple medical conditions — have become an exciting possibility. Although it is tempting to assume that mRNA technology will eventually supplant all other vaccine platforms, we need to acknowledge that not every vaccine technology will work for every target, and uncertainties and questions remain surrounding long-term immune response durability of mRNA vaccines.

Applying the technology to therapeutic indications in the fields of immuno-oncology, rare disease, protein replacement or supplementation, and cell and gene therapy is not science fiction — it is the active pursuit of many leading mRNA biotechnology companies. Optimizing and modulating delivery and expression of mRNA to meet the dosing needs of a therapeutic as opposed to a vaccine, will lead the way to wider applicability of this modality.

Gene therapy for metabolic diseases, heart disease and immuno-oncology are currently in the pipeline of the major biopharmaceutical companies that are developing mRNA therapeutics. In this application of the technology, mRNA is administered to the patient to compensate for a defective gene or protein, or to supply a therapeutic protein.

In addition, mRNA technology can be used to enhance cell therapy. The mRNA is transfected into ex vivo cells to alter the cell phenotype or function, and then these cells are reintroduced into the patient to treat the underlying disease. Clinical trials of mRNA-enhanced cell therapy are currently in progress for the treatment of melanoma and myasthenia gravis.

Overcoming activation of the innate immune system, which is a boon for mRNA vaccines, also will be key to honing mRNA therapeutics where immune activation is counterproductive. Newer biotech companies are on the cutting edge of this revolutionary frontier by creatively reimagining the structure — and hence expression — of mRNA for therapeutics.7

Conclusion

Groundbreaking mRNA technology has ushered in an exciting chapter in the history of medicine. There are clear advantages of mRNA technology in the vaccine field, especially in a pandemic setting, while research gaps still exist in optimizing the technology and expanding its use beyond vaccines. Other mRNA technologies also will add to the breadth of new approaches. The research community has only begun to explore the potential applications of mRNA technology, but the possibilities are inspiring with future breakthroughs expected.

Author Biographies

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Anusha Streubel, MD, MPH *is Executive Medical Director, PPD Clinical Research Services, Thermo Fisher Scientific. As part of the global product development vaccines team, she provides medical and scientific expertise, with a focus on clinical development strategies. She has provided medical leadership, expertise and oversight for multiple vaccine development programs, specializing in mRNA technology across therapeutic areas in both pediatric and adult populations.*

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