RNA VACCINES PART 1:
EXPLORING FUTURE POTENTIAL

SPOTLIGHT

What's next for mRNA vaccines?

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"...the synthetic nature of the mRNA technology will streamline R&D timelines and reduce costs."

VIEWPOINT

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Vaccines have had a substantial impact on human health for centuries. Yet, several major challenges have persisted, including improving existing but suboptimal vaccines, addressing unmet needs, responding rapidly and effectively to emerging infectious disease outbreaks, and simplifying and accelerating vaccine research and development (R&D) processes in order to get life-saving products faster to people who need them. This has provided the impetus for developing new technologies for delivering vaccines, such as mRNA.

The remarkable successes achieved with severe acute respiratory syndrome coronavirus

2 (SARS-CoV-2) mRNA vaccines, as seen by their efficacy and the speed with which they were brought to bear on the pandemic, has demonstrated the potential for addressing all of the challenges listed above. The key attributes of mRNA that may enable this are 1) mRNA encoding the antigen is delivered into cells of the vaccinated individual, leading to expression of the antigen *in situ* similar to that which happens during live virus infection and resulting in the induction of potent and broad-based immunity, and 2) mRNA vaccines utilize synthetic production methods not involving cell culture (unlike all other types of vaccines), thereby markedly simplifying and accelerating the means by which vaccines can be manufactured and characterized.

CHALLENGES & SOLUTIONS

Despite these advantages, there are two main areas of challenge for broader application of mRNA vaccines – technical and logistical. First, the effectiveness of mRNA products for diverse disease indications will depend on several technical factors relating to gene expression and immune stimulation. For gene expression, the optimum kinetics, duration, and location of therapeutic protein production are likely to be quite different for a preventive vaccine than for a gene therapy application. The same is the case for the ideal magnitude and type of immune stimulation needed, where a cancer vaccine will require a much stronger innate immune stimulus than a protein replacement therapy. mRNA vaccines do not yet represent a 'plug and play' platform technology that can be directly applied to any new product. Rather, almost certainly each new product will require optimization, including the nature of the mRNA molecule, type of delivery system, design of the antigen insert, and methods for production and characterization.

These technical challenges will be addressed through a deeper understanding of the mechanisms of action of the different types of mRNA vaccines (conventional, self-amplifying, circular) so that rational approaches can be taken to increase their utility and best apply them to the appropriate disease targets.

However, overcoming technical hurdles is not enough. To achieve the maximum population benefit of effective vaccines they must be deployed quickly, broadly, and affordably. This will require large-scale on-demand production capabilities and infrastructure, both in the developed and developing world. Furthermore, to facilitate widespread distribution of mRNA vaccines to all regions of the world, increased stability will be critical – particularly at high ambient temperatures.

These logistical roadblocks will be addressed via increasing the number of vaccine doses available by production scale-up and/or reducing the dose of mRNA required for effectiveness, the discovery and application of new formulations and delivery systems to increase potency and thermostability, and investment in infrastructure and technology transfer of knowhow to establish research, development and manufacturing capabilities in the developing world, which can then be applied to diseases of local importance.

Besides broadening the use of the mRNA technology to other vaccine targets, exciting advancements are being applied to non-infectious diseases, such as:

1. Gene editing using mRNA to deliver CRISPR/Cas tools *in situ* to correct genetic abnormalities in live animals, as well as ex *vivo* using cell-based therapies;
2. Personalized cancer immunotherapies have been substantially facilitated due to the increased speed with which tailor-made mRNA products can be produced and administered to patients in a timely manner, and;
3. The early but encouraging development of circular RNA as a therapeutic modality, which owing to its inherent stability may lead to more durable gene expression and be particularly valuable as gene therapy.

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THE NEXT 10 YEARS

The success of SARS-CoV-2 mRNA vaccines has stimulated substantial interest and investment in the technology. In fact, more than 70 mRNA vaccine programs against SARSCoV-2 alone are in various stages of preclinical and clinical development, according to the World Health Organization [1]. The large resource and intellectual capital currently being applied, the large design space available, the strong incentives provided by a return on these investments, and the major human health benefits of broader implementation of the mRNA technology will be strong driving forces for success. As a result, within 5–10 years major advancements up to and including licensure of new mRNA-based products will be achieved for other infectious disease targets (both preventive and therapeutic), cancer immunotherapy (including off-the-shelf and personalized approaches), gene therapy, and gene editing. In addition to addressing these unmet medical needs, the synthetic nature of the mRNA technology will streamline R&D timelines and reduce costs.

It is unlikely that a 'one size fits all' solution using mRNA will be attainable. There is no question that mRNA has become an important part of the vaccine technology toolbox, but it will not in the foreseeable future obviate the need for established approaches, such as live attenuated and inactivated viruses, viral vectors, and protein subunits. Rather, innovation in the areas described earlier will be required to effectively address the many unmet medical needs awaiting enabling vaccine technologies. However, the recent announcement by Moderna on the protective efficacy of a mRNA vaccine to prevent Respiratory syncytial virus disease in older adults in phase 3 clinical trials [2] – to a degree similar to that previously reported by GSK and Pfizer with their protein-based RSV vaccines – is an encouraging sign that mRNA vaccine technology even in its present form will have some successes beyond SARS-CoV-2.

BIOGRAPHY

JEFFREY B ULMER, PhD spent more than 30 years in vaccines R&D at Merck Research Laboratories, Chiron Corporation, Novartis and GlaxoSmithKline. His most recent leadership positions included Global Head, External R&D; Head, Preclinical R&D; and Program Head, Technical R&D. His scientific focus has been vaccine technology platforms, including DNA and mRNA vaccines, viral vectors, and adjuvants. He received his PhD in biochemistry from McGill University and completed his postdoctoral training in the laboratory of Nobel laureate Dr George Palade in the Department of Cell Biology at Yale University School of Medicine. He has published over 210 scientific articles, is an inventor on 11 patents, and is a Fellow of the International Society for Vaccines where he serves as Treasurer. He is currently President, TechImmune LLC (Newport Beach, CA) and Chief Scientific Advisor, Immorna Biotherapeutics (Morrisville, NC).

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AUTHORSHIP & CONFLICT OF INTEREST

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