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Opinion

What’s Next for mRNA Vaccines?

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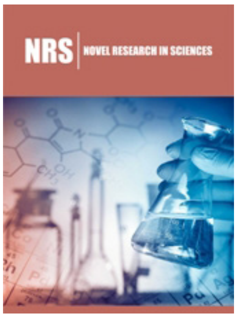
ISSN: 2688-836X



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Submission: October 14, 2021

Published: November 29, 2021

Volume 10 - Issue 1

How to cite this article: Joseph F Murphy. What’s Next for mRNA Vaccines?. Nov Res Sci. 10(1). NRS. 000726. 2021.
DOI: 10.31031/NRS.2021.10.000726

Introduction

The recent COVID-19 pandemic has shone a spotlight on a revolutionary technology called messenger RNA (mRNA). What is not so well known is that mRNA has been in the research and development sphere for about three decades. Now that the Pfizer/BioNTech and Moderna vaccines have been shown to be both safe and effective, researchers expect to be able to use this technology to create rapid-response vaccines in the future. Not alone do the mRNA vaccines have the potential to swiftly combat viral pandemics, but also generate promising treatments in other strategic areas, such as immunology, oncology, and rare diseases. Personalized Medicine [1].

There is currently a growing emphasis on the field of personalized medicine [2]. This concept creates treatment modalities that are tailored to a specific patient, as opposed to more conventional broad-based treatments. mRNA technology can be incorporated into this personalized medicine approach [3].

One of the pioneering companies responsible for developing the mRNA COVID-19 vaccine, BioNTech, was originally focused on developing anti-cancer vaccines. These mRNA vaccines educate the immune system to recognize specific antigens on the cell surface [4]. With COVID-19, this antigen is the spike protein expressed on the surface of the virus. The same reasoning is applied to training the immune system to recognize proteins on the surface of aberrant cells, such as cancer. For immunotherapy, this personalized medicine approach directs the immune system to:

A. Generate highly specific antibodies directed against the aberrant cellular antigens.

B. Train the adaptive immune system to mount an immune response against the disease.

The key element in this personalized medicine approach is to find the right target antigen, a target that is unique to aberrant cells and not normal cells. Various diseases create mutated proteins that the immune system recognize as foreign and mounts an immune response [5].

The approach involves genetically analyzing a tissue sample (biopsy) from a patient and individually tailoring a mRNA vaccine that then instructs the patients cells to produce these proteins. These vaccines that target tumor-associated (TAAs) or tumor-specific antigens (TSAs) then direct the immune system to specifically attack and destroy malignant cells that overexpress the antigens and achieve chronic therapeutic response because of immunologic memory [6]. Cancer vaccines are an attractive alternative immunotherapeutic option as they offer a specific, safe, and tolerable treatment.

Application of mRNA technology

One of the original drawbacks of the mRNA technology was that it was difficult to insert the mRNA into the cell. This problem was circumvented by using synthetic RNA and enveloping the material in lipid nanoparticles that can enter cells [7]. Major technological innovations like this have enabled mRNA to become a more feasible vaccine candidate. Various modifications of mRNA backbone and untranslated regions make mRNA less RNase- sensitive, more stable, and highly translatable. Improved purification methods have allowed mRNA products free of double-stranded contaminations, thus reducing the non- specific activation of innate immunity. More efficient *in vivo* delivery of mRNA has been achieved by formulating mRNA into delivery vehicles, including but not limited to lipid nanoparticles (LNPs), polymers, and peptides. mRNA encoded neoantigens have become the frontrunner in the personalized vaccine approach [8].

In addition to the safety and efficacy profiles of the approved vaccines, another major advantage of the mRNA vaccines is their relative simplicity to manufacture. In contrast to conventional vaccines that may require enormous bioreactors, mRNA vaccines can be produced in a test tube. It is produced in a cell-free system that does not require animal derived raw materials; therefore, the risk of contamination is lower than that observed with other complex vaccine processes. Moreover, the non-integrative nature and relatively transient expression inside the cells favors the mRNA safety profile.

Summary

mRNA technologies have responded successfully to the challenges of the COVID-19 pandemic. Several different vaccines are currently being developed for various diseases that are based on mRNA, with the potential to become available within a few years.

Currently, over twenty mRNA-based immunotherapies have entered clinical trials with some promising outcomes in solid tumor treatments. To further improve the potency of mRNA anticancer vaccines, other clinical trials are also ongoing to evaluate the combination of mRNA vaccines with either cytokine or checkpoint inhibitor therapies. To date, the data suggest that mRNA vaccines offer a powerful platform whose continued development will dramatically strengthen our ability to combat cancer.

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