Focus on mRNA Vaccine—A New Era in Vaccinology

mRNA vaccines represent a promising alternative to conventional vaccine approaches because of their high potency, capacity for rapid development and potential for low-cost manufacture and safe administration.

IntegrateRNA
A Division of Creative Biogene

https://integraterna.creative-biogene.com/
info@creative-biogene.com

What Is mRNA Vaccine?

The concept for the development of an mRNA vaccine is rather intelligible. After the antigen of choice from the pathogen target is identified, the gene is sequenced, synthesized, and cloned into the DNA template plasmid. mRNA is transcribed *in vitro*, and the vaccine is delivered to the subject. The mRNA vaccine utilizes the host cell machinery for *in vivo* translation of mRNA into the corresponding antigen, thereby mimicking a viral infection to evoke potent humoral and cellular immune responses. The final cellular location of the antigen is determined by the transmembrane domain and signal peptide. And the antigen can be expressed as intracellular, secreted, or membrane-bound protein. Given its fully synthetic nature, almost any sequence could be designed *in silico*, synthesized, delivered as an mRNA vaccine, and tested rapidlyin animal models.

Mechanism of mRNA Vaccines

Unlike a normal vaccine, RNA vaccines work by introducing an mRNA sequence which is coded for a disease specific antigen. Once produced within the body, the antigen is recognised by the immune system, preparing it to fight the real thing.

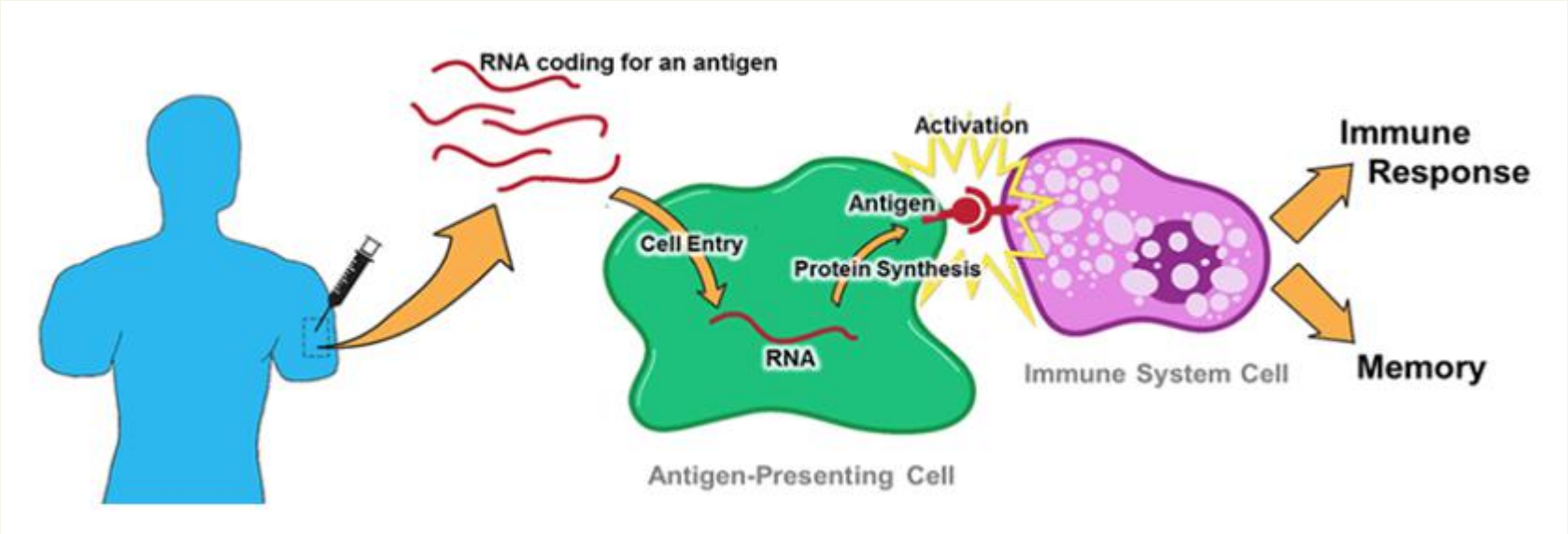


Figure 1. Mechanism of mRNA vaccines

Classification of mRNA Vaccines

Optimal mRNA stability and cell uptake;

Cytosolic delivery and mRNA expression in target cells;

Elicitation of the desired protective adaptive immune response for vaccines when the correlates of protection are known, such as for the influenza vaccine;

There is no potential risk of infection or insertional mutagenesis.

Classification of mRNA Vaccines

- **Non-replicating mRNA**

The simplest type of RNA vaccine, an mRNA strand is modified, packaged and delivered to the body, where it is taken up by the body's cells to make the antigen.

- ***In vivo* self-replicating mRNA**

The pathogen-mRNA strand is packaged with additional RNA strands that ensure it will be copied once the vaccine is inside a cell. This means that greater quantities of the antigen are made from a smaller amount of vaccine, helping to ensure a more robust immune response.

- ***In vitro* dendritic cells non-replicating mRNA**

Dendritic cells are extracted from the patient's blood, transfected with the RNA vaccine, then given back to the patient to stimulate an immune reaction.

Advantages and Challenges of mRNA Vaccines

mRNA vaccines have gained much interest in vaccinology owing to their numerous advantages. This versatile technology can achieve strong humoral and cellular immune responses, has intrinsic self-adjuvant properties, and results in transitory protein translation in a cell-cycle-independent manner. With the absence of pre-existing vector immunity that can interfere with subsequent vaccinations, as well as a manufacturing process done by an enzymatic/cell-free reaction, this technology offers faster, simpler, and cheaper operations than conventional vaccines do.

	Advantages	Challenges
mRNA Vaccines	Rapid research and development, mRNA vaccine production only takes 40 days	Under physiological conditions, mRNA is unstable and easy to degrade
	There is no need for any nuclear localization signal and transcription	Trigger an unnecessary immune response
	It will not be integrated into the genome to avoid possible therapeutic mutations	Safety and effectiveness need to be verified

Strategies for Optimizing mRNA Pharmacology

Many technologies are currently used to improve the pharmacological aspects of mRNA. The various mRNA modifications used and their impacts are summarized below.

- ✓ Synthetic cap analogues and capping enzymes stabilize mRNA and increase protein translation by binding to eukaryotic translation initiation factor 4E (EIF4E);
- ✓ Regulatory elements in the 5'-untranslated region (UTR) and the 3'-UTR stabilize mRNA and increase protein translation;
- ✓ Poly(A) tail stabilizes mRNA and increases protein translation;
- ✓ Modified nucleosides decrease innate immune activation and increase translation;
- ✓ Separation and purification techniques: RNase III treatment and fast protein liquid chromatography (FPLC) purification decrease immune activation and increase translation;
- ✓ Sequence and codon optimization increase translation;
- ✓ Modulation of target cells: co-delivery of translation initiation factors and other methods alters translation and immunogenicity.

Progress in mRNA Vaccine Delivery

Efficient *in vivo* mRNA delivery is crucial to achieving therapeutic relevance. So far, there are two basic methods for the delivery of mRNA vaccines that have been described, 1) loading of mRNA into DCs *ex vivo*, followed by re-infusion of the transfected cells; 2) direct parenteral injection of mRNA with or without a carrier. *Ex vivo* DC loading enables precise control of the cellular target, transfection efficiency and other cellular conditions; however, as a form of cell therapy, it is an expensive and labor-intensive approach to vaccination. Direct injection of mRNA is comparatively rapid and cost-effective, but it does not yet allow precise and efficient cell-type specific delivery.

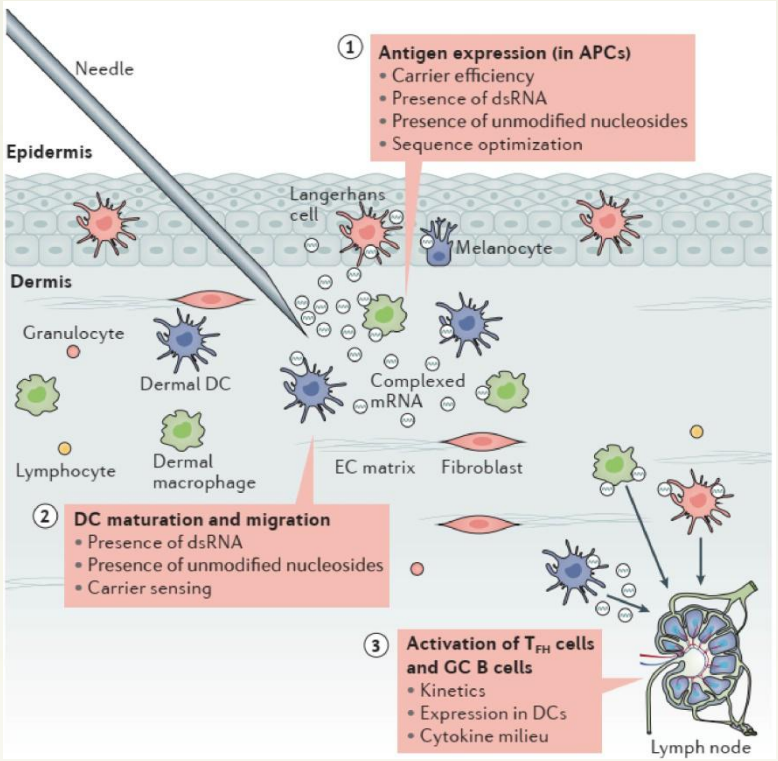


Figure 2. Considerations for the effectiveness of a directly injected mRNA vaccine.

Application of mRNA Vaccines

mRNA vaccines against infectious diseases

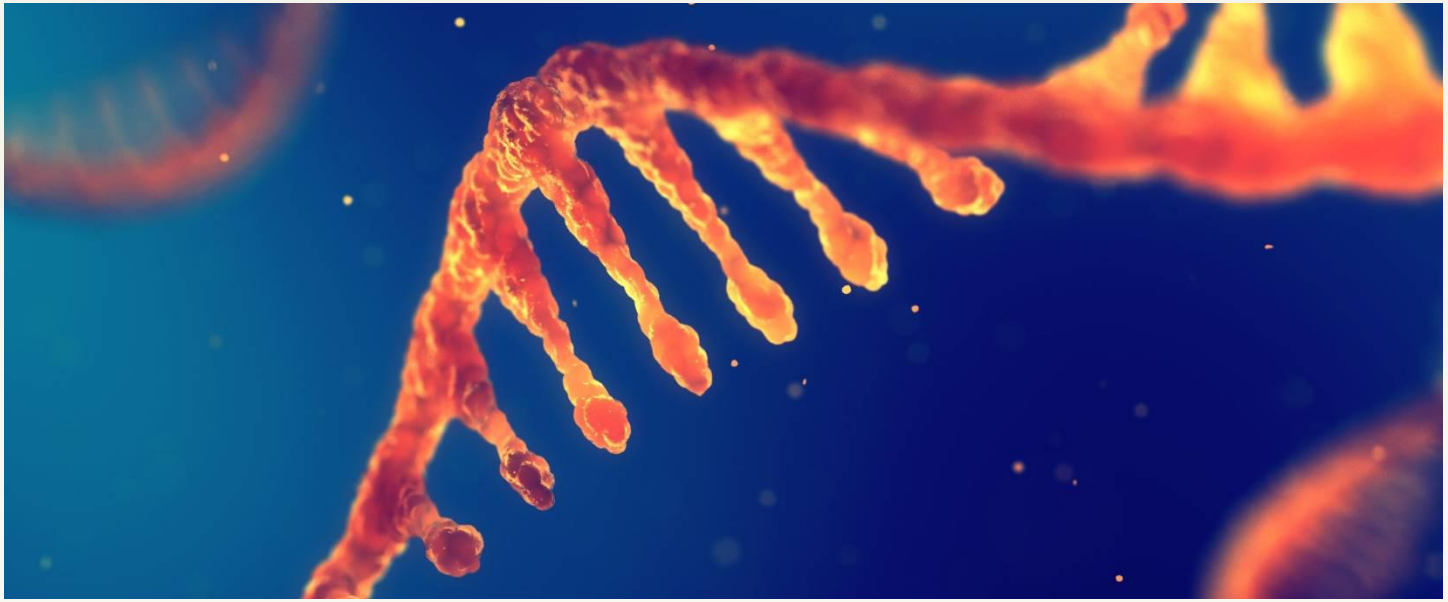
mRNA vaccines have elicited potent immunity against infectious disease targets in animal models and humans. For example, it's demonstrated that a self-amplifying mRNA vaccine encoding rabies virus glycoprotein induced an immune response and provided protection in mice and could potentially be used to prevent rabies in canine. Moreover, there are now sixteen prophylactic mRNA vaccines in clinical trials, to against HIV-1, rabies virus, zika virus, influenza virus and cytomegalovirus.

mRNA cancer vaccines

Cancer vaccines are a form of immunotherapy, where the vaccine triggers the immune system into targeting the cancer. Both dendritic cell vaccines and personalised cancer vaccines, where the RNA sequence in the vaccine is designed to code for cancer-specific antigens, are being explored. Over 50 clinical trials are currently underway for RNA vaccines in number of cancers, including blood cancers, melanoma, glioblastoma (brain cancer) and prostate cancer.

Conclusions and Future Directions

mRNA-based vaccines are a promising platform with the potential to be highly versatile, potent, scalable, streamlined, inexpensive, and cold-chain free. More importantly, mRNA-based vaccines may fill the gap between emerging pandemic infectious diseases and a rapid, abundant supply of effective vaccines. The mRNA vaccine technology has a huge potential over conventional vaccines. Nevertheless, it is still too early to fully understand its safety and effectiveness in humans. Further insights into the mechanism of action are needed to understand the impact of innate immune responses generated both by the mRNA and the delivery system, and to determine how learning from animal species will translate to humans.



THANK YOU

https://integraterna.creative-biogene.com/
info@creative-biogene.com