EClinicalMedicine 32 (2021) 100746

Contents lists available at ScienceDirect

EClinicalMedicine

journal homepage: https://www.journals.elsevier.com/eclinicalmedicine

Commentary

mRNA vaccines: A matter of delivery

Yuhong Cao[a], George F. Gao[b,c,*]

[a] CAS Key Laboratory for Biological Effects of Nanomaterials and Nanosafety, National Center for Nanoscience and Technology, Chinese Academy of Sciences, Beijing 100190, China
[b] CAS Key Laboratory of Pathogen Microbiology and Immunology, Institute of Microbiology, Chinese Academy of Sciences, Beijing 100101, China
[c] Chinese Center for Disease Control and Prevention, Beijing 102206, China

ARTICLE INFO

Article History:
Received 19 January 2021
Accepted 20 January 2021
Available online xxx

Vaccines based on messenger RNA (mRNA) are attracting worldwide attention as the *Pfizer* and *Moderna* vaccines have been authorized for emergency use by the U.S. Food and Drug Administration and similar authorities around the world. This is the first time that mRNA-based vaccines have ever been approved for use on healthy population [1], and marks a critical milestone for achievement in both science and public health. mRNA vaccines are a new form of vaccines that trigger immune responses by transfecting synthetic mRNA encoding viral antigens into human cells. Once the mRNA molecules are in the cytosol, the transfected cells translate the genetic information to the specific viral antigens. These antigens are then presented on the cell surface where they can be recognized by the immune cells [2]. mRNA vaccines have several advantages in comparison with conventional vaccines usually containing inactivated (or live attenuated) disease-causing organisms, protein peptides or DNA fragments made by antigens. Firstly, mRNA-based vaccines can be rapidly developed. They can be developed within days or months based on sequencing information from a target virus, while conventional vaccines often take years and require a deep understanding of the target virus to make the vaccine effective and safe. Secondly, these novel vaccines can be rapidly produced. Due to high yields from in vitro transcription reactions, mRNA production can be rapid, inexpensive and scalable. Thirdly, vaccine risks are low. mRNA does not contain infectious viral elements that pose risks for infection and insertional mutagenesis.

The development of mRNA vaccines has its roots in the 1990 demonstration of protein production from synthetic mRNA administrated in mice for the first time by researchers at the University of Wisconsin, USA [3]. Their subsequent work showed that the administration of vasopressin encoding mRNA in rat brains could elicit a physiological response. While the initial report was promising, it did not attract much attention from the pharmaceutical industry, largely because of concerns associated with the triggering of unwanted innate immune response, and the instability of the mRNA product. After 15 more years of effort, in 2005, Drs. Kariko and Weissman found an effective way to evade the innate immune response by modifying the mRNA's nucleosides [4]. This major breakthrough completely altered the pharmaceutical potential of mRNA therapies and resulted in substantial investment in associated research, leading to important discoveries in mRNA modification and purification to reduce the innate immune response and improve mRNA stability.

The challenge for effective application of mRNA vaccines lies in the delivery at both the micro and macro levels. Naked mRNA is rapidly degraded by extracellular RNases, it can be immunogenic, and alone, it cannot penetrate cell membranes to be transcribed in the cytosol. Thus, intracellular delivery is essential to facilitate cellular uptake of mRNA and to protect it from RNase degradation. To date, numerous delivery methods have been developed, including *ex vivo* loading of dendritic cells, physical delivery methods, cationic peptide protamine, and cationic lipid nanoparticles (LNPs) delivery, among which LNPs seems to be the most appealing and commonly used tool [2]. LNPs often consists of four components: (1) cationic or ionizable lipids, smart macromolecules that can be functionalized to improve the entrapment of mRNA, to increase cellular uptake efficiency, and promote endosomal escape; (2) lipid-anchored polyethylene glycol (PEG), which is used for reducing particle sizes, preventing particle aggregation, increasing circulation time and reducing uptake by untargeted cells; (3) cholesterol that stabilizes LNPs complexes; and (4) phospholipids, which support lipid bilayer structure [2]. Although each of the LNPs' components has been under intensive study for LNPs delivery optimization using different formulation expertise, challenges, such as inefficient transfection and nonspecific targeting, remain for bringing the full potential of mRNA vaccines into play. Continuing research into diverse delivery platforms is still a priority to guide the development and optimization of intraellular delivery systems.

The authorization of mRNA vaccines for use is only the first of many steps to achieving effective application and success in battling the current pandemic. At the macro-level, transportation, storage, physical and human logistics are just as crucial. The *Pfizer* vaccine, which requires storage at −80 °C for quality control, needs to be transported in special freezers from the company hubs in Michigan and Wisconsin, USA, to distribution centers across the country and then to designated vaccination centers and the arms of individuals. Every single step needs diligent care and coordination. The *Moderna*

E-mail address: gaofu@chinacdc.cn (G.F. Gao).

https://doi.org/10.1016/j.eclinm.2021.100746

vaccine has simpler requirements, with storage at −20 °C also makes transportation and storage a big challenge. The two-week interval required for the second shot of both vaccines also adds to the storage and transportation challenge for ensuring widespread vaccination. Future research needs to focus on the degradation mechanisms of mRNA and the design and transformation of mRNA molecules and LNPs complexes to address the challenge.

The safety of the novel vaccines must also be evaluated. The side-effects reported from clinical trials of the *Pfizer* vaccine include incidences of Bell's palsy, pain at the injection site, fatigue, chills and fever [1], and those from the *Moderna* vaccine include pain at the injection site, muscle aches and headaches. Though most of these are not life-threatening, a few severe allergy-like reactions have been reported after vaccination with the *Pfizer* vaccine. PEG, a chemical component in LNPs is thought to be the culprit allergen [5]. mRNA-based approaches were first designed to treat cancer and are now being rapidly repurposed to vaccinate a healthy population. Unexpected life-threatening events may occur [2], even if at very low frequency, and intensive safety monitoring is essential for safe guarding the success and learning for future events.

The challenges of deploying the novel mRNA vaccines for use in the current pandemic make use extremely difficult under the conditions prevailing many developing countries. Other types of vaccines based on different scientific approaches require less demanding storage and transportation conditions than mRNA-based vaccines and can be expected to be approved for use where appropriate to jointly tackle the worldwide pandemic.

The COVID-19 mRNA vaccines are indeed a milestone success for gene therapy and prophylaxis, opening opportunities for a wide range of medical and clinical applications. They can be expected to contribute enormously to both public health and curing a range of severe diseases, including cancers and genetic disorders [2].

Declaration of Competing Interest

The authors declare no conflict.

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