Chapter 4

Development and Technology of mRNa Vaccines and Therapeutics beyond COVID-19

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Abstract

This study is based on the application of mRNA vaccines for the treatment of various infectious diseases and different cancer types. An mRNA vaccine is a new type of vaccine that introduces cells into the human body that produce harmless protein to trigger the immune system to develop immunity-producing antibodies against antigens. These vaccines were developed after the global outbreak of COVID-19. This significantly helped the scientists to invent vaccines in a short period of time compared to the traditional vaccines. The main role is to reduce the death rate by controlling the spread of disease. In the case of cancer, mRNA vaccines help the immune system to recognize and destroy the cancer cells by producing the tumor-specific antigens. In order to create targeted mRNA technology, including its applications in vaccines, immunotherapies, protein replacement therapy, and genome editing as well as its distribution to particular cell types and organs.

Currently researchers are in their role to treat lung cancer, breast

cancer, and so on by providing personalized treatments. Since the mRNA vaccines do not contain live pathogens, they are safer to use and offer a promising future for cancer treatment.

Keywords: *mRNA vaccines, immunogenicity, antibodies, COVID-19, cancer immunotherapy.*

1. Introduction

The covid-19 pandemic was noted as a significant development of mRNA vaccines Moderna and Pfizer-BioNTech, which are major public health threats. The challenges in the distribution of COVID-19-based vaccines have most supplies in high-income countries, whereas low- and middle-income countries have the least access to them. The manufacturing capacity for future mRNA vaccines and therapeutics (e.g., human immunodeficiency virus, TB, dengue) and using local production of new lipids, enzymes, and other reagents. The mRNA technology also provides a novel approach to treat both communicable and non-communicable diseases as well as immune-related and non-immune diseases. Diseases like cancers, diabetes, and cardiovascular and respiratory conditions are experiencing an epidemiological transition. This mainly focuses on a comprehensive mRNA-based vaccine and its therapeutic use in clinical development in which it is part of the WHO-MPP mRNA technology transfer program.

1.1 History and Development of mRNA Vaccination

mRNA, which is known as a messenger of RNA, acts as a messenger by carrying the genetic information from DNA to ribosomes, where the proteins are synthesized. It was first discovered by Sydney Brenner, François Jacob, and Matthew Meselson in 1961.

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This mRNA made a tremendous change in our current lifestyle. Besides the disadvantages like instability of mRNA molecules, rapid degradation by the enzyme, and difficulty in delivery, it is one of the most promising innovations in modern biotechnology.

In 1990, it was proved by the scientist that the prepared synthetic RNA could be injected into the mouse muscle cells to produce proteins. Hence, mRNA could be used to instruct cells to make specific proteins inside the body.

During 2005, scientists Katalin Karikó and Drew Weissman discovered that changing the nucleoside in the messenger RNA reduces the immune reactions by preventing the immune system from recognizing the mRNA as a foreign invader. Our immune system uses PRRs, which are known as pattern recognition receptors, like TLR3, TLR7, and TLR8 (Toll-like receptors). These receptors play an important role in detecting the foreign RNA, e.g., viruses. They recognize unmethylated single-stranded or double-stranded RNA. After modifying it with N1-methyl pseudouridine or pseudouridine, the modified bases look similar to those that are present in mammalian RNA. Therefore, it allows them to bypass the detection by these pattern recognition receptors. This innovation made mRNA safer and more effective for medical use.

1.2 Later Technologies

Scientists developed LNP, which is known as Lipid Nanoparticle Technology. They are critical, versatile drug delivery systems.

mRNA vaccines: The covid-19 mRNA vaccines were only possible due to LNP technology. They improve therapeutic efficacy.

2. mRNA DEVELOPMENT BEYOND COVID-19

mRNA vaccine technology utilizing lipid nanoparticles for delivery is expanding rapidly beyond Covid-19. Allowing for rapid development of vaccines and therapeutics for both communicable and non-communicable diseases.

2.1 Cancer immunotherapy

Previous research focused on using mRNA to trigger the immune response against tumors. Current research is based on the personalized vaccines that target specific neoantigens in a patient's tumor. Instead of directly killing the tumor cells, these vaccines stimulate the immune system to recognize and destroy the cancer cells.

2.2 Mechanism involves

An mRNA cancer vaccine contains messenger RNA encoding tumor-associated antigens and is administered into the body. After administration, the mRNA enters the body cells and instructs them to produce the tumor antigen. This activates T-cells (T-lymphocytes), which are white blood cells of the immune system that mature in the thymus and protect the body from pathogens and cancer.

Activation: They are activated in the second lymphoid organs, like lymph nodes, where they encounter specific antigens presented by other immune cells, like dendritic cells. Activated T-cells recognize and destroy the cells by expressing the same antigen.

Merits of mRNA vaccines in cancer immunotherapy include the following:

- They are capable of personalized cancer treatment based on the

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patients.

- Highly specific targeting of tumor antigens
- These vaccines are noninfectious because no live viruses were used and are therefore safe to use.
- Well known for their ability to produce a strong immune response.
- They can be rapidly designed and manufactured
- Demerits of mRNA vaccines in cancer immunotherapy include the following:
- They are expensive for personalized vaccines
- They are still under clinical research for many cancers.

Companies like Moderna and BioNtech are currently working on personalized mRNA cancer vaccines by conducting clinical trials

3. Applications Beyond COVID-19

- It has been proven that it is effective in treating cancer and infectious disease.
- The therapeutic as well as the preventive roles of mRNA technology have been used in the treatment of infectious diseases.
- mRNA vaccines have several applications for various human infectious diseases caused by pathogens such as arboviruses (dengue and chikungunya), HIV, and rabies.

3.1 Advantages of Mrna Vaccines

- The main advantage of mRNA vaccines is the speed at which the vaccines can be designed and manufactured in response to pathogens.

- mRNA vaccines are developed in the lab by synthesizing an infectious disease virus's genetic material by testing and manufacturing the newly discovered infectious disease.
- In Phase III trials the Pfizer-BioNTech (BNT162b2) and Moderna (mRNA1273) vaccines were more than 90% Effective in preventing symptomatic COVID-19
- According to efficacy, mRNA vaccines have cellular immune responses, and they are very strong against infectious diseases, cancer, and autoimmune disorders.
- Another benefit of mRNA technology is personalized cancer vaccines. Tumors have mutagens or neoantigens that can be targeted with mRNA vaccines, and the immune system destroys the cancer cells without affecting the normal cells.

3.2 Limitations of Mrna Vaccines

- The ultra-cold storage has only been distributed in limited regions because of its high cost.
- Innovative methods such as lyophilized (freeze-dried) formulations or thermostable LNPS are active to defeat this barrier.
- The unstable mRNA should be stored in extremely cold conditions to prevent its degradation. The Pfizer-BioNTech COVID-19 vaccine was to be stored at -70°C (-94°F), while the modern vaccine was to be stored at -20°C (-4°F).
- In low-income countries, the cold chain storage was not available, leading to a lack of vaccines.

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- In clinical trials, the mRNA has mild to moderate side effects such as infection
- site pain, fatigue, and headache and a serious reaction like anaphylaxis in rare conditions.
- mRNA vaccines are costly. So if they are not distributed in low-income countries, it will lead to a lack of distribution of vaccines.

3.3 Other Major Applications of mRNA Vaccines Includes

3.3.1 Cardiovascular Technology

mRNA is emerging as a therapeutic approach for cardiovascular disease by delivering genetic instructions to cells to promote tissue repair and reduce fibrosis. The current research aims to treat myocardial infarction, which is a heart attack, and heart failure and ischemia. The process includes lipid nanoparticles delivering mRNA directly to cardiomyocytes to treat conditions like heart failure.

3.3.2 Genetic Disorder

- mRNA therapy treats the genetic disorder by delivering the synthetically modified mRNA through LNP cells.
- mRNA acts as a blueprint and instruction to create necessary proteins and address the disease caused by protein deficiencies.
- It focuses on the rare metabolic disorders, e.g., methylmalonic acidemia and Fabry disease.

3.3.3 Methylmalonic acidemia

It is a rare inherited metabolic disorder characterized by the body's inability to properly break down certain proteins and fats, causing toxic methyl malonic acid to accumulate in the blood and tissues.

4. Fabry Disease

It is a rare, x-linked genetic lysosomal storage disorder caused by a deficiency of the alpha-galactosidase enzyme.

4.1 Infectious disease

mRNA vaccines are being developed to protect against several infectious diseases like influenza, malaria, and meningitis.

4.2 Autoimmune diseases

- mRNA plays an important role in autoimmune disease.
- Patients with autoimmune inflammatory rheumatic diseases are at high risk for infections and can use mRNA vaccines, which have high efficacy.

5. Structure and Components of mRNA Vaccines

- The structure of the mRNA vaccine mainly focuses on delivering the genetic information safely into the cells so that they will be able to produce the specific antigens in the immune system to stimulate an immune response.
- mRNA being a nucleic acid (polymer of nucleotides). It consists of a ribose sugar, a phosphate group, and a nitrogenous base like adenine, uracil, guanine, and cytosine.
- mRNA (Messenger RNA): It is the major and an important active component of the vaccine, which is responsible for protein synthesis inside the human body.
- It contains genetic instructions for producing a viral antigen protein. Eg: spike protein, which is responsible for covid-19.
- It consist of a 5' cap, 5' UTR, coding region, 3' UTR, and 3'

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poly(A). Tail.

5'cap

7-methyl guanosine is added to the 5' end and protects it from degradation by exonuclease and assists in ribosome binding.

5'UTR

Which is a 5' untranslated region. It is a region between the 5' cap and the start codon that regulates translation and stability.

Translation : It is the process of carrying the genetic information from DNA to ribosomes for protein synthesis.

Coding region: The coding regions are composed of codons, which will be coding for the specific amino acid. It starts with a start codon (AUG) and ends with a stop codon (UAA, UAG, or UGA).

3'UTR (untranslated region): This region is located after the stop codon. They act as binding sites for proteins and microRNAs that dictate when, where, and how much protein is produced from a transcription.

Poly(A) Tail: A string of 50-250 adenine nucleotides added to the 3' end that protects the molecule from degradation and increases the translation process efficiently.

6. Conclusion

Based on the above study, it is proved that mRNA plays a significant role in the current medical technology. They provide a safe, efficient, and rapid method for preventing various diseases. From the outbreak of Covid-19 and still now, it has been useful in various ways for the treatment of infectious disease, genetic disorder, and autoimmune disorder.

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