

mRNA Vaccine Platforms in Cancer Immunotherapy: Mechanisms, Innovations, and Clinical Prospects

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ABSTRACT

Cancer is one of the primary causes of global health issues and deaths. To address this burden and to develop alternatives to chemotherapy and radiation, innovative and targeted treatment strategies must be developed. One way to do this is through cancer immunotherapy, which is quickly becoming an innovative approach that uses the body's immune system to identify and destroy cancer cells. Within the immunotherapy realm, mRNA vaccines have quickly gained full attention due to their safety, adaptability, and rapid timeline to produce. The mechanism of action of mRNA vaccines for cancer is based on the introduction of synthetic mRNA containing either tumor-related or tumor-specific antigens that induce local generation of the antigenic protein once introduced into the host cell, especially dendritic cells. In turn, the target proteins generated from the injected synthetic mRNA are presented through Class II Histocompatibility Complex (MHC) pathways, which promote both cellular- (CD8⁺ cytotoxic T cells) and humoral-mediated immunity targeting tumor cells. A significant advantage of the mRNA vaccination approach is to create a potent and specific anti-tumor immune response without causing significant harm to healthy tissues (non-infectious); thus supplying a promising platform for cancer therapy. In the past several years, advances in mRNA design capabilities, including both structural optimization and the addition of modified nucleosides, and advances in effective vaccine delivery systems (such as lipid nanoparticles), have provided substantial improvements in stability and efficacy of delivery of mRNA vaccines. Furthermore, personalized mRNA vaccines targeting patient-specific neo-antigens represent a significant breakthrough in the evolution of precision medicine. Ongoing challenges with mRNA vaccines apply to four general areas: (1) mRNA instability due to chemical and physical properties, (2) delivery efficiencies of mRNA, (3) tumor heterogeneity, and (4) immunosuppressive tumor microenvironments. Ongoing clinical research and clinical trials are evaluating ways to overcome these hurdles as well as evaluation of combination therapies of mRNA vaccines with immune checkpoint inhibitors and/or other therapies. In summary, mRNA vaccines represent a unique and rapidly evolving strategy within the field of cancer immunotherapy and have the ability to dramatically change the future of cancer treatments and create more options for targeted and personalized therapies for individuals with cancer.

Keywords: mRNA vaccines; Cancer immunotherapy; Tumor-associated antigens (TAAs); Neoantigens; Lipid nanoparticles (LNPs); Antigen-presenting cells (APCs); CD8⁺ T cells; Personalized cancer vaccines; Precision oncology

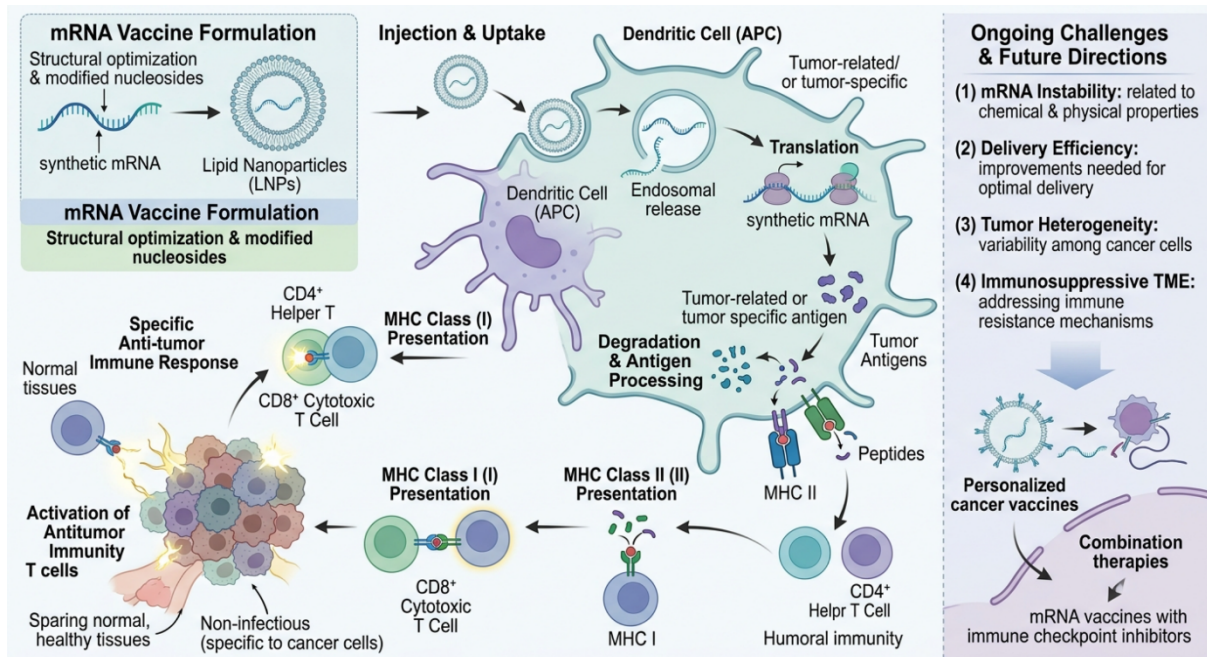
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Graphical Abstract



1. Introduction

Cancer is still one of the leading causes of death around the world and is a huge burden on public health systems and economies. Millions of new cancer cases are diagnosed every year globally, and even with advancements in diagnostic and therapeutic technologies, a large proportion die from their cancer. Traditional cancer treatment modalities include surgery, chemotherapy and radiotherapy; while they have increased the number of people surviving, there are many limitations to using these approaches to treat cancer, including: a lack of specificity; systemic toxicity; development of resistance; and recurrence. Due to these limitations, more innovative methods of treating cancer that are more targeted and more effective and safer have been developed[1].

Cancer immunotherapy has started to change the way we think about how to use the immune system to fight cancer. Unlike how traditional medicines kill cancer cells by directly targeting them, immunotherapy works by increasing the immune system's ability to identify and kill cancer cells. The immune system has built in ways to find abnormal cells in the body through using antigens. Cancer cells are often able to produce abnormal proteins that can be used as antigens (tumor associated antigens [TAAs] or tumor specific antigens [TSAs]). For example, neoantigens are produced as a result of genetic mutations. All of these antigens can be

targeted by the immune system and should be destroyed by it [2].

Because cancer cells are very adaptable and have many ways to escape detection by the immune system, they must find new ways to avoid destruction. Immune checkpoint molecules, such as PD-1 (Programmable Death 1) and CTLA-4 (Cytotoxic T Lymphocyte Antigen 4), disrupt the immune system (?) and ability of tumor cells to be eradicated leading to the progression of cancer. These modifications have led to the creation of immunotherapeutic approaches such as immune checkpoint inhibitors, monoclonal antibodies, adoptive T cell therapy, and cancer vaccines[3].

Cancer vaccines have received much attention because they can create a targeted and long-lasting immune response to tumor cells. Unlike preventive vaccines for infectious diseases, therapeutic cancer vaccines are designed to create an immune response to tumor-specific antigens and can therefore be used to reverse the progression of cancer by targeting tumor antigens (antigens that are on the surface of cancer/tumor). Within the category of therapeutic cancer vaccines, mRNA-based cancer vaccines are emerging as an innovative and promising platform[4].

The principle behind mRNA vaccines is to introduce synthetic mRNA molecules that code for specific antigens into host cells and to use the production of proteins resulting from the translation of mRNA to produce proteins that are similar to the tumor antigen

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and cause an immune response. mRNA vaccine technology has gained wide acceptance due to the rapid development, efficacy, and safety seen through the use of mRNA vaccines developed for COVID-19. In oncology, this success demonstrated using mRNA COVID-19 vaccines has increased interest in using mRNA vaccines as a therapeutic cancer vaccine[5].

Within the field of vaccination technology, mRNA cancer vaccines offer multiple unique benefits compared with traditional vaccine platforms. First, mRNA viruses are not infectious viruses, so there is no associated risk with using live or live attenuated viruses as vaccine platforms. The mRNA technology offers a great safety profile, since mRNA does not include itself in the genomics of its host. One of the key advantages of mRNA vaccines is that they can be developed and manufactured quickly based on the sequence data for tumor-associated antigens.

The efficiency of the delivery system of mRNA vaccines (e.g., lipid nanoparticles (LNPs), which can serve as nanocarriers) should be improved to develop mRNA vaccines. LNPs will protect mRNA from degradation due to enzymatic mechanisms and deliver mRNA to cells; thus improving the stability of mRNA and the efficiency of translation. Also, additional modification of mRNA will promote the immunogenicity and stability of mRNA vaccine products (e.g., optimized codons, modified nucleosides, improved UTRs, etc.) [6].

Development of mRNA cancer vaccines presents many clinical translation challenges. mRNA can be unstable, they require ultra-cold storage before administration, their efficiency of delivery is poor, and tumors produce an immunosuppressive environment. Despite these challenges, multiple clinical trials continue to demonstrate the efficacy of mRNA vaccines in treating cancer, particularly melanoma, lung, and pancreatic.

Combination of mRNA vaccines with other immunotherapeutic modalities (e.g., immune checkpoint inhibitors) may lead to a synergistic effect whereby resistance to immune-mediated tumor destruction is improved and therefore patient outcomes are improved. Advances in genomics and bioinformatics have facilitated the identification of personalized neoantigens for creating personalized mRNA cancer vaccines.

The advent of mRNA vaccines represents an exciting new avenue in cancer immunotherapy. mRNA vaccines, given their ability to generate targeted immune responses and their favorable

safety profile and flexibility could play a major role in the future of cancer therapy. Continued scientific advancement will allow mRNA vaccines to transform the treatment of cancer and to provide patients with improved quality and duration of life[5].

2. Mechanism of Action and Immunological Basis

mRNA cancer vaccines use the basic principles of molecular biology and immunology to generate an immune response against cancer while avoiding the introduction of any pathogenic materials (i.e., actual viruses or bacteria). They attend to the need for a controlled and directed activation of the immune system, like the body's natural response to a pathogen.

Synthetic mRNA containing genetic instructions for the creation of either non-tumor-associated or tumor-associated antigens; this mRNA will ultimately be expressed in the host's body to stimulate a protective immune response against the cancerous tissues. Upon vaccination, synthetic mRNA is taken into the cells of the host (mainly, the antigen presenting cells or APCs, including dendritic cells) using mRNA delivery systems (lipid nanoparticles), which facilitates the internalization of mRNA using endocytosis [7].

Once inside an APC, the mRNA is transported out of the endosome into the cytoplasm and then translated into mRNA proteins by ribosomes. After translation has occurred, the APC processes and breaks down the mRNA proteins into peptide fragments, which are then loaded onto MHC (major histocompatibility complex) molecules.

MHC Class I will present the mRNA antigens to CD8+ Cytotoxic T Lymphocytes (CTLs). MHC Class II will present the mRNA antigens to CD4+ Helper T Cells. One important step in the development of an anti-tumor immune response is the activation of the CD8+ T Cells. Activation of CD8+ T Cells allows for identification of and binding to the MHC-peptide-antigen complex displayed by the cancer cells; this allows for CTL-mediated induction of apoptosis of the cancer cells through release of toxic proteins (i.e., perforin and granzymes) from the CTLs to the cancer cells. CD4+ helper T-cells can promote immune responses through the secretion of cytokines that support the activation and proliferation of CTL's as well as B-cells. In addition to providing an immune response via cellular immunity, mRNA vaccines can also provide an immune response through Hummoral Immunity by activating B-cells that can produce

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antibodies. Specifically, B-cells will recognize antigens associated with tumor cells, differentiate into plasma cells, and produce antibodies. These antibodies can attach to the surface of tumor cells and then reinforce the destruction of those tumor cells through mechanisms such as Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC) [8]. One of the goal of mRNA vaccines, in addition to inducing a robust immune response, is to create immunological memory by developing memory T-cells and B-cells as a result of the immune response. Memory T-cells and B-cells provide long-term protection against tumor formation and are critical to preventing the recurrence of tumors after treatment because of the potential for relapse (recurrence of a tumor), which is very common in the treatment of cancers.

The immunological response to mRNA vaccines is dependent on multiple factors including the structure of the mRNA, the method used to deliver the mRNA into the body, and the activation of the innate immune system. The mRNA can activate innate immune receptors such as Toll-Like Receptors (TLR's), resulting in the secretion of type I Interferon and other cytokines that enhance the immune response, but overactivation can decrease the efficiency of mRNA translation. Thus, it is important that the design of mRNA be optimized to reduce excessive activation of the innate immune system.

Many mRNA vaccines have incorporated modified nucleosides, such as pseudouridine, to reduce the innate immune activation and increase the stability of mRNA. Also, optimizing UTR and codon usage will help increase the efficiency of mRNA translation and increase protein production.

The delivery method of mRNA into the body plays a critical role in whether or not the mRNA vaccine is successful. Currently, lipid nanoparticles are the most common carrier used to deliver mRNA because they efficiently protect the mRNA from degradation, increase cellular uptake of the mRNA, promote endosomal escape of the mRNA. The advancements in nanotechnology have allowed researchers to develop even more effective and targeted delivery systems for mRNA.

The tumor microenvironment (TME) is also an important factor in determining the efficacy of mRNA vaccines. The TME contains many immunosuppressive cell types (e.g., regulatory T-cells [Tregs], myeloid derived suppressor cells [MDSCs]), which suppress the immune response.

Therefore, it is essential that these obstacles are overcome to induce a robust and effective anti-tumor immune response[9].

Combination therapies, which comprise of mRNA vaccines and immune checkpoint inhibitors, have shown promise for overcoming inhibiting the immune response. Immune checkpoint inhibitors work by blocking proteins such as PD-1 and CTLA4, which can reverse the inhibition of T-cells and facilitate an effective immune response to mRNA vaccines.

mRNA cancer vaccines act through a combination of molecular and immunological processes. Through the induction of robust cellular and humoral immune responses and generating immunological memory, mRNA cancer vaccines provide an innovative and highly effective method of treating cancer.

3. Types, Components, and Formulation Strategies

mRNA Cancer Vaccinations can be broken up into a few different groups based on both structure and how they work. Within Two main groups of Vaccination, classified by non-replicating mRNA vaccines (Simple) and self-amplifying mRNA vaccines (More complex). Non-replicating (simple) mRNAs contains mRNA only that encode for the antigen the vaccine will be targeting. Their other properties rely on the cells to which they enter being able to take the information contained in the mRNA and create the proteins. Because they only need to be designed/crafted with mRNA, they are quicker to create and manufacture and are good for personalized treatment development. Self-amplifying mRNA vaccines have the mRNAs with additional pieces incorporating some virus genomics to create mRNA replicated inside each of the delivered target cells[10]. This has higher amounts of the target protein made as well as improved immune responses. However, they are more difficult to create and design, and will likely require additional safety considerations.

The mRNA vaccine design process involves several critical components. In regard to the sequence of the mRNA, it will contain the information encoded by the sequence that precedes each amino acid (the antigen that will be constructed). Optimization of the mRNA sequence is critical for maximum efficiency in the construction of an antigen. The cap structure that exists at the 5' end of the mRNA is responsible for the stability and initiation of the translation of the mRNA. There exist UTR (untranslated regions) that are present to provide regulation for the mRNA

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(stability during transport, and to assist in translation efficiency). The polyA tail is used to enhance the stability of the mRNA and prevent degradation. The delivery system of the mRNA vaccine is also a critical component in formulation. Whereas lipid nano-particles (carriers) are the main vehicles currently being utilized, there exists multiple types of lipid nano-particles (composed of ionizable lipids, cholesterol, phospholipids, and PEG-lipids), that can carry/encapsulated mRNA within, and protect against degradation, and help the target cells to take in the mRNA. The overall formulations of mRNAs strive to ensure the mRNA is adequately stabilized, delivered effectively, and immunogenic. The advances in nanotechnology allow there to be more targeted delivery vehicles to selectively deliver the mRNA to specific cells/tissues. This will improve how well the vaccine works and reduce the amount of side effects. New and existing stabilization methods (lyophilization) are continually being researched to attempt to overcome the significant challenge(s) posed with the storage of mRNA Vaccines (i.e., ultra-cold storage requirements). The ability to keep medicines or vaccines in ultra-cold environments for distribution is a very large limitation, particularly where distributing from resource-limited environments[11].

4. Clinical Applications, Challenges, and Future Prospects

of different cancers including, but not limited to, melanoma, lung cancer, breast cancer, prostate cancer, and pancreatic cancer. These early-stage studies (phase I and II), particularly with melanoma patients, demonstrate some evidence that personalized mRNA vaccine therapy enhances overall survival compared to standard treatment.

Although these outcomes look promising, there are a number of obstacles to overcome in order to bring mRNA cancer vaccines into mainstream clinical practice. These include: (1) mRNA itself is an instable molecule, thus requiring robust delivery systems; (2) manufacturing of mRNA is expensive and must be resolved for widespread deployment; and (3) (a) tumors have a very heterogeneous nature and (b) are capable of employing a variety of immune evasion mechanisms as they develop, therefore influencing the efficacy of mRNA vaccines.

Personalized mRNA vaccines represent a major breakthrough in cancer therapy. By sequencing a patient's tumor and identifying neoantigens, custom-

made mRNA vaccines can be made for each patient, enhancing the specificity of the therapy whilst minimizing potential off-target side effects.

The future direction of mRNA cancer vaccines will be entirely reliant upon the development of combination therapies with current therapies, improving the delivery system, and advances in genomics and bioinformatics. Combining mRNA vaccines with immune checkpoint inhibitors and other forms of immunotherapy is predicted to enhance the effectiveness of these therapies.

mRNA vaccine platforms have the capacity to revolutionize cancer therapy. Continued innovation and optimization of the current available resources is critical to overcome existing barriers and ultimately fully utilize the therapeutic potential of mRNA vaccine platforms[12].

5. Advantages of mRNA Cancer Vaccines

Advances in cancer therapy have been achieved through the introduction of mRNA cancer vaccines, which offer multiple biological and manufacturing advantages compared to standard treatment modalities. mRNA technology's advantages are considered fundamental components of personalized and precision medicine.

The main benefit of mRNA cancer vaccines is their specificity, thus potentially minimizing or eliminating any anti-tumor activity, that may affect non-cancerous tissue. In general, mRNA vaccines specifically target cancer or neoantigens (tumor antigens). Conversely, chemotherapy and radiation are not selective and can destroy both cancerous and non-cancerous cells. Thus, mRNA vaccines can be administered utilizing tumor-specific antigens or neoantigens, which leads to fewer off-target effects and a decreased overall toxicity due to the specific targeting of tumor-associated antigen populations. Additionally, the ability to create mRNA constructs that have numerous target antigens allows for a broader range of immune responses to occur due to administering multiple antigens to the same heterogeneous tumor population (may have different antigenicity).

Lastly, the rapid production of mRNA vaccines is another significant advantage of their use as cancer therapies. The majority of standard vaccine platforms require lengthy manufacturing procedures (cell culture, purification of protein, creation of viral vectors, etc.); however, once the DNA sequence of the target antigen has been defined, mRNA vaccines can be manufactured rapidly through in vitro transcription of mRNA. The rapidity of mRNA

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vaccine manufacturing is also a critical factor in the development of an effective cancer treatment; time can be crucial in relation to developing a treatment plan [13].

In addition to their rapid production, mRNA vaccines have an overall positive safety record. The mRNA is a non-infectious acellular molecule, therefore not capable of causing insertional mutagenesis due to the lack of incorporation into the host genome. Furthermore, there are no long-term safety concerns related to the use of an acellular entity as the cellular metabolism will degrade mRNA once it has been translated. By having a short-lived expression, these vaccines can be restricted and not remain present in the body longer than necessary to provide protection.

Another major advantage of the mRNA platform technology is its flexibility and adaptability because altering a single step in the manufacturing process (the sequence of the encoded mRNA) can allow for many different vaccines to be produced, thereby making the technology very flexible to many different types of cancer. In addition, it is possible to create a personalized cancer vaccine that targets the specific mutations of a person's tumor.

The ability of mRNA vaccines to generate both cellular and humoral immune responses is also a significant benefit. CD8⁺ cytotoxic T cells are activated to kill tumour cells directly, whereas CD4⁺ helper T cells and B cells act as immune regulators and generate antibodies. By generating two types of immune response activation the overall effectiveness of the treatment will be enhanced [14]. The use of lipid nanoparticles (LNP) as delivery systems for mRNA vaccines complements the advantages of using these technologies for vaccine development. These LNPs protect the mRNA from enzymatic degradation and therefore allow for efficient uptake into the target cells. In addition, LNPs can act as adjuvants themselves and increase the immune stimulatory responses without the addition of other immune stimulatory agents.

In the long term mRNA vaccines support scalability and cost-effectiveness. Although the initial costs of producing mRNA vaccines will be high, the standardised process of manufacturing along with the elimination of biological systems will eliminate variable production and allow for large scale production of mRNA vaccines.

Additionally, mRNA vaccines have a high compatibility with combination therapies. They can be safely combined with immune checkpoint

inhibitors, chemotherapy, radiotherapy, or targeted therapies to achieve better therapeutic results. Combinations of therapies improve the ability of mRNA vaccines to overcome tumour immune evasion and thus increase response rates.

An additional emerging advantage is the incorporation of self-amplifying mRNA that can increase the amount of the antigen generated in target cells by reducing the amount of dose required and thus improving immune responses. This innovation will provide for greater vaccine efficacy and greater cost-effectiveness.

The advantages of mRNA vaccines for the treatment of cancer include their specificity, safety (low potential for adverse effects), rapid development time, flexibility of manufacturing process, and strong immune induction, therefore, these vaccines are an exciting and important option for modern oncology[15].

6. Limitations and Challenges

The research being done on mRNA cancer vaccines is very promising. However, before mRNA cancer vaccines will be in full use within clinics, many scientific, technical, clinical, and manufacturing problems must be resolved.

The biggest challenge concerning mRNA vaccines is their instability. RNases (Ribonucleases) occur naturally in our environment and break down mRNA, so mRNA is highly susceptible to degradation in the body. Protective delivery mechanisms (lipid nanoparticles) can enhance the stability of administered mRNA, but it can still be difficult to store and transport as the mRNA degrades during post-delivery.

Due to the instability associated with mRNA vaccines, many of them need to be stored at an ultra-cold temperature of -70 degrees Celsius long enough for the vaccine to be safe to administer. The logistics of proper shipping and storage at this temperature in developing countries may be extremely difficult due to low capacities to meet the cold chain requirement. Researchers are developing mRNA vaccines with thermally stable formulations that could allow for refrigerated or room-temperature shipping and storage.

Another challenge associated with mRNA vaccine development is that properly delivering mRNA to APCs remains a priority for researchers. The effective use of lipid nanoparticles will improve how mRNA is delivered; however, making sure that mRNA is only delivered to APCs and properly targeting APCs will be more important aspects of the

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research. If mRNA is consumed by other types of cells, there may not be enough for the appropriate number of APCs to create sufficient immune reaction [16].

In addition to the aforementioned issues related to delivering mRNA vaccines, tumors are often found to have immunosuppressive intracellular environments that also inhibit vaccine efficacy. The tumor microenvironment is composed of regulatory T cells, myeloid-derived suppressor cells and immunosuppressive cytokines that negatively affect both the activation and function of immune cells. Therefore, the immunogenicity of mRNA cancer vaccine will often be significantly negatively impacted by the immunosuppressive components within the TME.

The issues associated with responding effectively to mRNA cancer vaccines is made particularly challenging by the variety of different antigens present on the surface of various cancer cell types. Thus, if the immune system is to respond to an antigen, there may also be the potential for an immune system escape (not recognizing the cancer cells or the indications of its existence) for the remaining patient after the immune system has produced an effective immune response.

When mRNA vaccines are used as a cancer treatment, there may be potential challenges associated with producing an effective immune response because the majority of oncogenes are derived from endogenous genes. Therefore, when the immune system identifies these antigens, they will generally trigger an immune tolerance. Thus, to instigate an effective immune response against the specific antigens, the correct antigen must be selected. Additionally, the design of the mRNA vaccine must also concentrate the immune system on the antigen of interest.

Additionally, researchers providing mRNA to patients will need to consider any adverse immune response that may develop following mRNA administration. Findings indicate that there are relatively few problems associated with mRNA vaccines being used as long as there is not an excessive activation of innate immune response within the recipient. Excessive amounts of inflammation in the recipient's body as a result of hasty activation of their innate immune system may impede the translation of the administered mRNA. Therefore, balancing maximal immunogenicity against minimal tolerogenicity will be critical to the successful use of mRNA cancer vaccines.

The manufacturing of mRNA vaccines should be considered from a business point of view. mRNA is expensive to produce and create in a clinical-grade form with the proper lipid nanoparticle delivery mechanism. The clinical-grade state also requires special facilities and substantial quality control [17]. Another challenge contributing to the challenge of bringing a treatment to patients is the regulatory path; individuals requiring mRNA-based vaccines will require a custom plan for manufacturing and expedited approval. Guidelines for obtaining an approval from identified standards of care will be established, thus improving the delivery of mRNA cancer vaccines [18].

A need also exists for longer research data on the safety and effectiveness of mRNA cancer vaccines. Presently, the completed early clinical studies completed thus far have produced promising results; however, the long-term safety and efficacy of mRNA vaccines must be further assessed through rigorous larger clinical studies.

As these barriers to mRNA cancer vaccines are eliminated, multidisciplinary teams involving people versed in molecular biology, nanotechnology, immunology and regulatory science, will ultimately realize the potential of mRNA cancer vaccines. Continued funding in basic and applied research will be necessary to sustain innovation and overcome barriers that exist along the timeline to success of mRNA cancer vaccines[19].

7. Personalized mRNA Vaccines and Precision Oncology

One of the most exciting recent advancements within the field of oncology is personalized mRNA cancer vaccines. Personalized mRNA vaccines represent an innovative approach that fits within the framework of contemporary precision medicine; they are specifically designed to address an individual's unique tumor genetic profile and take a personalized approach rather than using a "one-size-fits-all" traditional treatment strategy[20, 21].

It begins with sequencing one's tumors and using next-generation sequencing (NGS) technologies to identify mutations present in cancer cells. Mutated cancer cells often create neoantigens (novel proteins that do not exist in normal cells) that may be perceived as foreign by the immune system[22].

After identifying the neoantigens, bioinformatics tools are utilized to analyze and evaluate the immunogenicity of the neoantigen. In addition to immunogenicity, bioinformatics can help select

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which neoantigens to encode into synthetic mRNA that will serve as the patient-specific vaccine to fight each patient's tumor.

Numerous advantages exist with this technology. The first is the specificity of the immune system will only recognize the versions of the mutated proteins expressed by tumor cells, which allows very specific targeting of the tumor and minimal impact on other tissues—reducing the likelihood of having off-target reactions or inducing autoimmunity. The second is when neoantigens are utilized as a target, there will be an increased likelihood that a robust immune response will occur because neoantigens are very highly immunogenic.

Clinical trials have produced encouraging data for personalized mRNA vaccines with melanoma patients. Personalized mRNA vaccines have resulted in enhanced immune response and decreased recurrence rates in patients receiving these vaccines. The combination of personalized vaccines with immune checkpoint inhibitors has resulted in increased efficacy from vaccines[23].

Nonetheless, personalized vaccines come with challenges. The time required to sequence, analyze, and produce the vaccine for each person results in a high expense, and rapid turn-around times are critical for maintaining relevance for patients with aggressively growing cancers.

The application of artificial intelligence (AI) and machine learning (ML) in predicting neoantigens and designing mRNA vaccines has dramatically improved the efficiency with which large datasets of neoantigens can be analyzed and how to design a vaccine to achieve optimal results.

Incorporating personalized mRNA vaccines into current medical practice represents an important step toward achieving precision oncology because these vaccines take an individual's tumor data and utilize it to design and deliver unique neoantigens as therapy[21].

8. Future Perspectives and Conclusion

There is a high level of optimism regarding the future of mRNA-based cancer vaccines due to advancement after advancement that is aimed at overcoming current restrictions and to allow for much greater clinical application.

Next generation delivery systems will be one of the most important areas of evolution with researchers looking at a variety of interesting new nanocarrier types (e.g., polymeric nanoparticles, lipid/polymer hybrid nanoparticles, exosomes) that will greatly

improve both the targeting and efficacy of their mRNA cancer vaccine products.

mRNA formulations that have improved "thermostability" will also be an important focus area within the mRNA vaccine framework. These formulations would be able to be stored at higher temperatures thereby reducing logistical barriers (e.g., temperature control requirements) and increasing the global availability of mRNA cancer vaccines.

The most important aspect of the future of mRNA-based cancer vaccines will be seen through combination therapies. It is anticipated that mRNA-based cancer vaccines will eventually be used in combination with:

- Immune checkpoint inhibitors
- CAR-T cell therapy
- Oncolytic viruses
- Conventional therapies

These combination therapies will serve to enhance immune responses and to combat resistance mechanisms that tumors utilize in defeating the immune system.

The combined use of developments in genomics, proteomics, and bioinformatics will further refine the identification of neoantigens during the development of mRNA cancer vaccine products. Additionally, the use of artificial intelligence-based platforms will significantly expedite the development of personalized medicine.

Regulatory agencies will need to adjust current regulatory frameworks in order to provide guidance for rapid, individualized therapies. For instance, plans for streamlined therapeutic product approval processes and adaptive clinical trial design will likely be required.

Overall, mRNA cancer vaccine technology provides for a paradigm shift in how to treat cancer. Due to their ability to develop safe, targeted, and individualized therapies, they will become foundational to future oncology therapies. While many challenges remain in regards to mRNA cancer vaccines, ongoing research, technological advances, and clinical evidence will generate support for these mRNA cancer vaccine technologies as standard of care therapies.

Ethical Declarations

Ethics Approval and Consent to Participate

Not applicable. This study is a review article and does not involve any human participants, animal experiments, or clinical data.

Availability of Data and Materials

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Author Contributions

All authors contributed significantly to the conception, design, literature review, drafting, and critical revision of the manuscript. All authors have read and approved the final version of the manuscript.

Declaration of Generative AI and AI-assisted Technologies

The authors declare that no AI-assisted tools were used in the writing, editing, or preparation of this manuscript. The content is entirely original and developed through human intellectual effort.

References

1. Mattiuzzi, C. and G. Lippi, *Current cancer epidemiology*. Journal of epidemiology and global health, 2019. **9**(4): p. 217-222.
2. Bray, F., et al., *The ever-increasing importance of cancer as a leading cause of premature death worldwide*. Cancer, 2021. **127**(16): p. 3029-3030.
3. Upadhyay, A., *Cancer: An unknown territory; rethinking before going ahead*. Genes & diseases, 2021. **8**(5): p. 655-661.
4. Printz, C., *Lung cancer new leading cause of death for women in developed countries: Data reflects increased rates of smoking*. Cancer, 2015. **121**(12): p. 1911-1912.
5. Gote, V., et al., *A comprehensive review of mRNA vaccines*. International journal of molecular sciences, 2023. **24**(3): p. 2700.
6. Pardi, N., et al., *mRNA vaccines—a new era in vaccinology*. Nature reviews Drug discovery, 2018. **17**(4): p. 261-279.
7. Du Pasquier, R.A., D.D. Pinschewer, and D. Merkler, *Immunological mechanism of action and clinical profile of disease-modifying treatments in multiple sclerosis*. CNS drugs, 2014. **28**(6): p. 535-558.
8. Schiller, M., et al., *Immune response modifiers—mode of action*. Experimental dermatology, 2006. **15**(5): p. 331-341.
9. Schmidt-Weber, C.B. and K. Blaser. *Immunological mechanisms in specific immunotherapy*. in *Springer seminars in immunopathology*. 2004. Springer.
10. Ramadan, E., A. Ahmed, and Y.W. Naguib, *Advances in mRNA LNP-based cancer vaccines: mechanisms, formulation aspects, challenges, and future directions*. Journal of Personalized Medicine, 2024. **14**(11): p. 1092.
11. Laila, U.E., W. An, and Z.-X. Xu, *Emerging prospects of mRNA cancer vaccines: mechanisms, formulations, and challenges in cancer immunotherapy*. Frontiers in immunology, 2024. **15**: p. 1448489.
12. Taibi, T., et al., *mRNA-based therapeutic strategies for cancer treatment*. Molecular Therapy, 2024. **32**(9): p. 2819-2834.
13. Rahman, M.M., N. Zhou, and J. Huang, *An overview on the development of mRNA-based vaccines and their formulation strategies for improved antigen expression in vivo*. Vaccines, 2021. **9**(3): p. 244.
14. Mohamad Razif, M.I., et al., *Emergence of mRNA vaccines in the management of cancer*. Expert Review of Vaccines, 2023. **22**(1): p. 629-642.
15. Wang, Y., et al., *mRNA vaccine: a potential therapeutic strategy*. Molecular cancer, 2021. **20**(1): p. 33.
16. Fu, Q., et al., *mRNA vaccines in the context of cancer treatment: from concept to application*. Journal of translational medicine, 2025. **23**(1): p. 12.
17. Zhou, F., et al. *From structural design to delivery: mRNA therapeutics for cancer immunotherapy*. in *Exploration*. 2024. Wiley Online Library.
18. Lu, L., X. Lu, and W. Luo, *Personalized Cancer Vaccines: Current Advances and Emerging Horizons*. Vaccines, 2025. **13**(12): p. 1231.
19. Miao, L., Y. Zhang, and L. Huang, *mRNA vaccine for cancer immunotherapy*. Molecular cancer, 2021. **20**(1): p. 41.
20. Yang, B., et al., *mRNA Cancer Vaccines: From Pandemic Paradigm to Personalized*

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- Oncology Therapeutics*. *Cancer Innovation*, 2025. **4**(6): p. e70041.
21. Jacob, E.M., J. Huang, and M. Chen, *Lipid nanoparticle-based mRNA vaccines: a new frontier in precision oncology*. *Precision clinical medicine*, 2024. **7**(3): p. pbac017.
 22. Huang, X., et al., *Personalized pancreatic cancer therapy: from the perspective of mRNA vaccine*. *Military Medical Research*, 2022. **9**(1): p. 53.
 23. Lin, F., et al., *Advancing personalized medicine in brain cancer: exploring the role of mRNA vaccines*. *Journal of Translational Medicine*, 2023. **21**(1): p. 830.