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A DETAILED REVIEW MRNA VACCINES TECHNOLOGY AND APPLICATIONS

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1. ABSTRACT

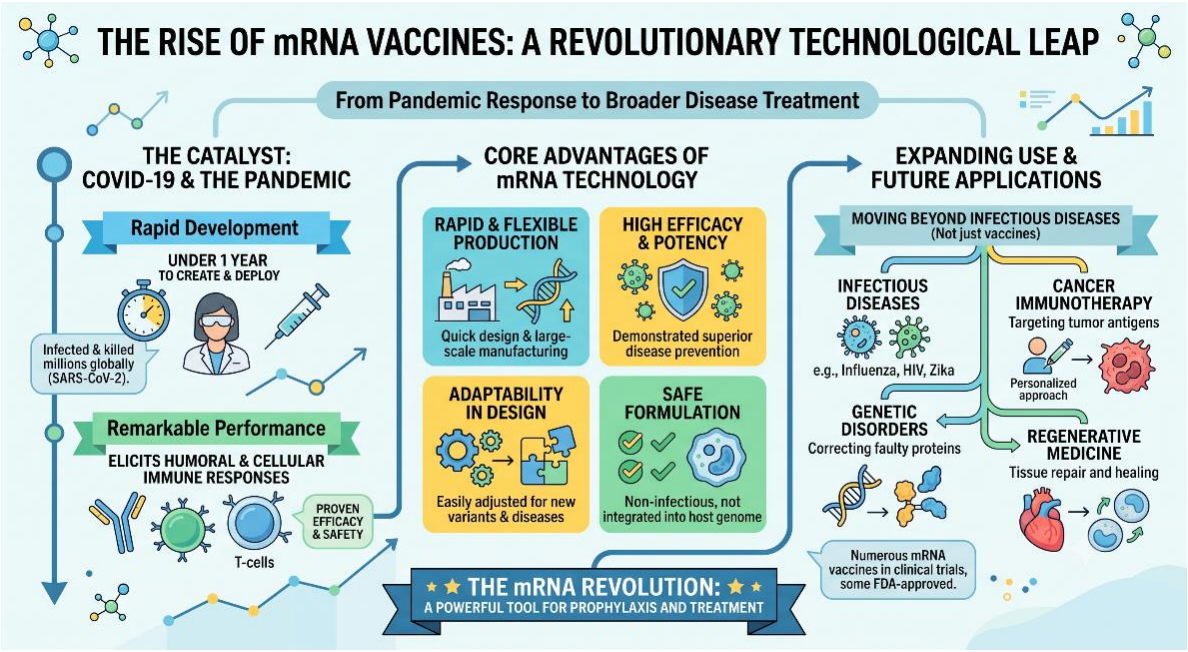
Due in great part, though not entirely, to their remarkable performance in recent years against the global pandemic COVID-19, mRNA vaccines have emerged as a very effective techniques in the prophylaxis and treatment of diseases. Despite minor issues with design, fabrication, and mode of administration, the pharmaceutical and biotechnology industries are encouraged to expand the use of mRNA vaccines to a wide range of diseases due to their enormous superiority in terms of efficacy, safety, and large-scale manufacturing.

Over the past ten years, the development of messenger RNA (mRNA) vaccines for therapeutic and preventive uses has advanced quickly. The mRNA vaccine has demonstrated therapeutic efficacy in a number of areas, including cancer, immunotherapy, infectious diseases, genetic disorders, and regenerative medicine. Numerous RNA vaccines have entered clinical trials, and a few have received FDA approval.

Millions of people have been infected and killed by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) that produced the coronavirus disease-19 (COVID-19) pandemic. Generating vaccines typically requires years of development and safety and efficacy testing. However, the creation and implementation of two mRNA vaccines took less than a year. The most promising vaccination candidates in the fight against the pandemic are mRNA vaccines with spotlights because of their quick production time, affordability, adaptability in vaccine design, and clinically demonstrated capacity to elicit humeral and cellular immune responses.

KEYWORDS: COVID-19, SARS-CoV-2, mRNA vaccination, effectiveness, and security.

GRAPHICAL ABSTRACT



2. NTRODUCTION

Rising global population (nearing 7.8 billion), higher population density, increased international travel, and human interactions facilitate the dissemination of new pathogens. Zoonosis poses a continual risk of bringing previously unidentified pathogens, like HIV, SARS, MERS Cov, and SARS-CoV-2, into the population. Vaccines represent the most economical approach to halt this worldwide transmission and to control both short-term and long-term infections. Traditional vaccines are usually categorized as live, weakened, or non-live. Vaccinating with weakened pathogens has effectively reduced the incidence of several infectious diseases, such as smallpox, polio, measles, mumps, and rubella. Traditional vaccines made from weakened viruses like these require years to create because of the time needed to gather and then modify (weaken) the virus in the lab. Adaptation can be hindered by several elements, such as the challenge of growing the pathogen in specific biosafety level laboratories. Additionally, alongside a tailored manufacturing process, every new traditional vaccine necessitates intricate purification and evaluation. In this context, live attenuated vaccines present a significant risk of reversion.

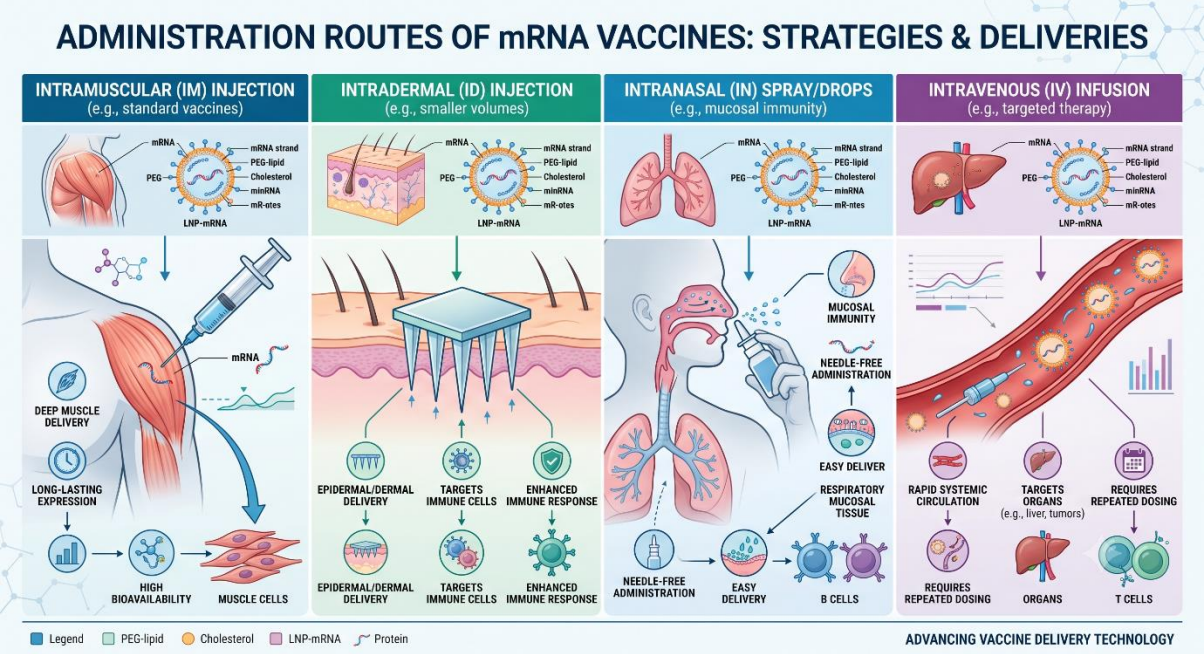
Cancer has emerged as a growing public health concern. In the United States, reports indicated that approximately 5370 new cases and 1670 fatalities daily are anticipated throughout 2023. Despite significant advancements made in recent decades to fight the feared disease, including the promising breakthroughs with immune checkpoint inhibitors (ICI), cancer continues to be a difficult medical issue impacting millions globally. Consequently, creating newer and more efficient platforms for cancer therapy has become an immediate necessity.

The antigenic element of non-live vaccines can consist of the entire inactivated organism, purified proteins obtained from the organism (e.g., diphtheria or tetanus toxoid), recombinant proteins like those in hepatitis B virus and human papillomavirus vaccines, or polysaccharides present in the pneumococcal vaccine for Streptococcus pneumonia. Non-live vaccines are frequently mixed with adjuvants to enhance their immunogenicity.

Historically, vaccine development is a complicated and costly process that is slow and labour-intensive, needing significant financial resources. Developing a new vaccine candidate with existing technologies is projected to exceed 500 million USD, with further costs ranging from 50 to 700 million USD necessary to upgrade manufacturing plants and machinery. In fact, the requirement for specialized production methods and facilities for every vaccine developed with traditional technologies maintains elevated validation and manufacturing expenses [1]. Moreover, the mean timeline for developing a standard vaccine from the preclinical stage exceeds 10 years and has a chance of market entry of 6%. The extended lead time and numerous potentially intricate steps involved in manufacturing emphasize the pressing need for innovative methods to accelerate vaccine development. Manufacturers urgently need new technologies that can enhance rapid vaccine creation and large-scale production, decrease costs, shorten licensing timelines, and enable swift responses to pandemic threats. Viral vector and nucleic acid-based vaccine platforms developed over recent decades offer potential solutions to these vaccine issues

3. Administration Routes for mRNA vaccines technology

The method of administering mRNA vaccines significantly influences the effectiveness of vaccination (Egger et al. 1999). Figure 1 illustrates the frequently utilized injection pathways, which encompass intradermal (ID), subcutaneous (SC), intramuscular (IM), intranasal (IN), and intravenous (IV) delivery. Alternative methods, including intranasal injection, intravaginal injection (Lindsay et al. 2020), and intratumoral injection, were examined as well. Due to the fact that immune cells and lymphoid organs are typical targets for vaccination, the anatomical and physiological characteristics of the injection sites (skin, muscle, lymphoid organ, and systemic circulation) can influence a vaccine's safety and effectiveness. This information aids in selecting the administration route when deciding on the type (conventional or self-amplifying) and the delivery format (carrier-mediated, naked, or cell-based) of the mRNA vaccine.



Administration routes of mRNA vaccines: strategies & deliveries

Intradermal (ID) injection administers mRNA vaccines straight into the dermis area, which consists of dense connective tissue. Antigen-presenting cells (APCs) found in the dermal tissue, including dermal dendritic cells (DCs) and macrophages, have the capability to internalize and process the mRNA vaccine. The blood and lymphatic vessels in this skin layer assist in delivering mRNA vaccines and APCs to the lymph nodes for T and B cell activation. Their findings indicated that ID vaccination using a needle-free device could generate a superior antibody response compared to IM injection. While ID injection provides favoured access to immune cells and lymphoid tissues and has demonstrated effectiveness in vaccination, its application has been constrained by a small injection volume and a significant risk of local side effects such as swelling, pain, erythema, and puritan. To enhance injection volume and mRNA dosage, participants underwent several ID injections at various locations during each visit in a clinical study.

Subcutaneous (SC) injection delivers mRNA vaccines to the sub cutis area beneath the epidermis and dermis. This skin layer primarily consists of a sparse arrangement of fat tissues and a limited number of immune cells in comparison to the dermis. In contrast to ID injection, the more flexible adipose tissue at the SC injection site allows for a greater injection volume, resulting in reduced pain and lower pressure. Furthermore, the increased injection volume might offset the less effective drainage function in this skin layer. It is important to mention that the absorption rate in the SC region is sluggish, potentially leading to unintended deterioration of the mRNA vaccine.

Intramuscular (IM) injection administers the vaccine into muscle tissue, which is located beneath the dermal and subcutaneous layers. Muscles possess an extensive network of blood vessels that can aid in recruiting and recirculating various immune cell types, including infiltrating APCs, to the site of

injection. A recent study showed that following the IM injection of mRNA encapsulated in LNPs, the radiolabeled mRNA was found at the injection site and in the draining lymph node for a minimum of 28 hours. Comprehensive flow cytometer evaluation revealed that APCs in muscle and both APCs and B cells in draining lymph nodes had the radiolabeled mRNA. The volume of IM injections exceeds that of ID injections in humans. Moreover, IM injections might lead to less severe local side effects than ID and SC routes. Consequently, IM injection is the most commonly utilized method for administering adjuvant vaccines.

Intravenous (IV) administration introduces mRNA vaccines into the bloodstream. The volume of IV injection is the greatest among the previously mentioned delivery methods. The overall quantity of protein generated through IV administration is typically the greatest when compared to other methods. Therefore, the IV method was selected for administering mRNA that encodes a neutralizing antibody when an effective concentration of the antibody was necessary in the bloodstream. Typically, LNPs administered via IV transport mRNA to the liver, particularly targeting hepatocytes, Chuffer cells, and liver endothelial cells, based on the various delivery carriers used. Furthermore, IV injections might provide direct access for mRNA vaccines to immune cells and lymphoid tissues in the bloodstream, potentially improving vaccination effectiveness. For instance, earlier research discovered that IV administration of mRNA vaccine focused on spleen DCs and triggered an immune reaction against tumours in mice. Although the benefits of IV injection noted earlier, the plasma proteins, enzymes, and mechanical forces in the bloodstream may obstruct the delivery of the vaccine. Additionally, the administration of mRNA and delivery vehicles into circulation could lead to systemic side effects, including spleen damage and lymphocyte reduction.

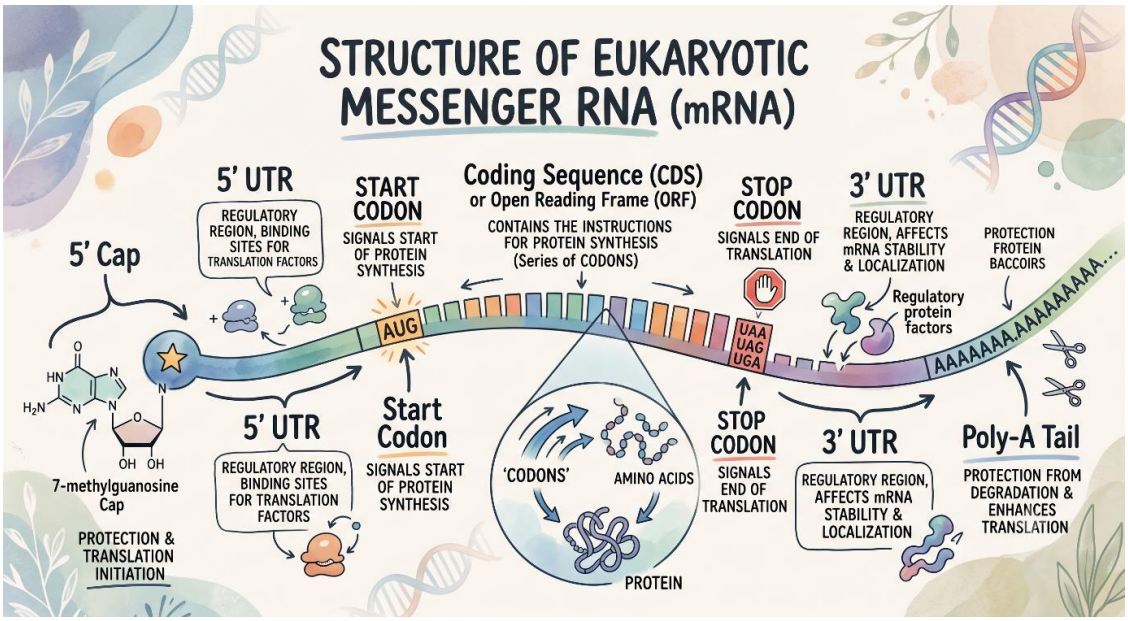
In summary, the biological characteristics of various administration pathways can influence the safety and effectiveness of vaccination. Table 1 outlines the characteristics of various primary delivery pathways for mRNA vaccines. A thorough comparison of various administration routes for a specific mRNA type and delivery carrier will aid in identifying the best injection method and enhance the creation of an effective mRNA vaccine.

4. Technology for Delivering mRNA

Successful in vivo delivery of mRNA is crucial for achieving treatment. Exogenous mRNA needs to traverse the lipid membrane barrier to enter the cytoplasm for conversion into functional protein (Figure 3). Two main factors influence the cytoplasmic availability of IVT mRNA. One reason is that numerous active Razes, present in the extracellular region of cells, can quickly break down IVT mRNA. The second is the cell membrane. It stops negatively charged large RNA molecules from passively entering the cytoplasm. Eukaryotic cells are capable of actively taking up naked mRNA; however, the uptake and cytoplasmic transfer rates are generally very low in most cell types (< 1/10000) (12). By using a delivery system, mRNA can be enhanced for better transfer efficiency and

safeguarded from nuclease degradation. Currently, there are three primary strategies for mRNA delivery (1): physical techniques that directly disrupt the cell membrane barrier; (2) virus-derived methods that leverage natural biological uptake mechanisms; (3) Nano carrier-mediated non-viral vectors that are carefully engineered and simple to produce.

Structure of mRNA



Several types of RNA are essential in the process of gene expression, which uses the information stored in DNA to create molecules like RNAs and proteins that are crucial for cell function [2].According to the central dogma of molecular biology, DNA is copied into mRNA, which is then used to make proteins [1].The mRNA is a copy of the DNA and acts as a guide for building proteins, as it holds the instructions for the sequence of amino acids that will form the protein [2,7].Moreover, each mRNA molecule includes non-coding or untranslated regions that help regulate how the mRNA is processed and read.

5. RNA Vaccines for the Prevention of Infectious Illness

Over the past twenty years, mRNA vaccines have been studied thoroughly for preventing infectious diseases, as well as for cancer prevention and treatment. Significant advancements have been achieved up to this point (19, 20). Cancer mRNA vaccines were developed to present tumour-associated antigens that activate cell-mediated immune responses to eliminate or suppress cancer cells (59). The majority of cancer vaccines are explored primarily as treatments rather than preventive measures and have been discussed in other sources (20, 60, 61). mRNA vaccines targeting infectious diseases may be created for either preventive or therapeutic use. mRNA vaccines that carry antigens from infectious pathogens elicit robust and powerful T cell and humeral immune responses (8, 16, 19). As mentioned earlier, the method for producing mRNA vaccines is completely cell-free,

straightforward, and quicker in comparison to the development of whole microbes, live attenuated, and subunit vaccines. This quick and efficient production method positions mRNA as a promising bio-product that could help bridge the gap between new infectious diseases and the urgent requirement for effective vaccines. Generating RNA on a large scale to meet commercial needs is the initial step in developing mRNA vaccines. At present, all necessary components for mRNA production are accessible at the GMP grade; however, certain components are provided in limited quantities.

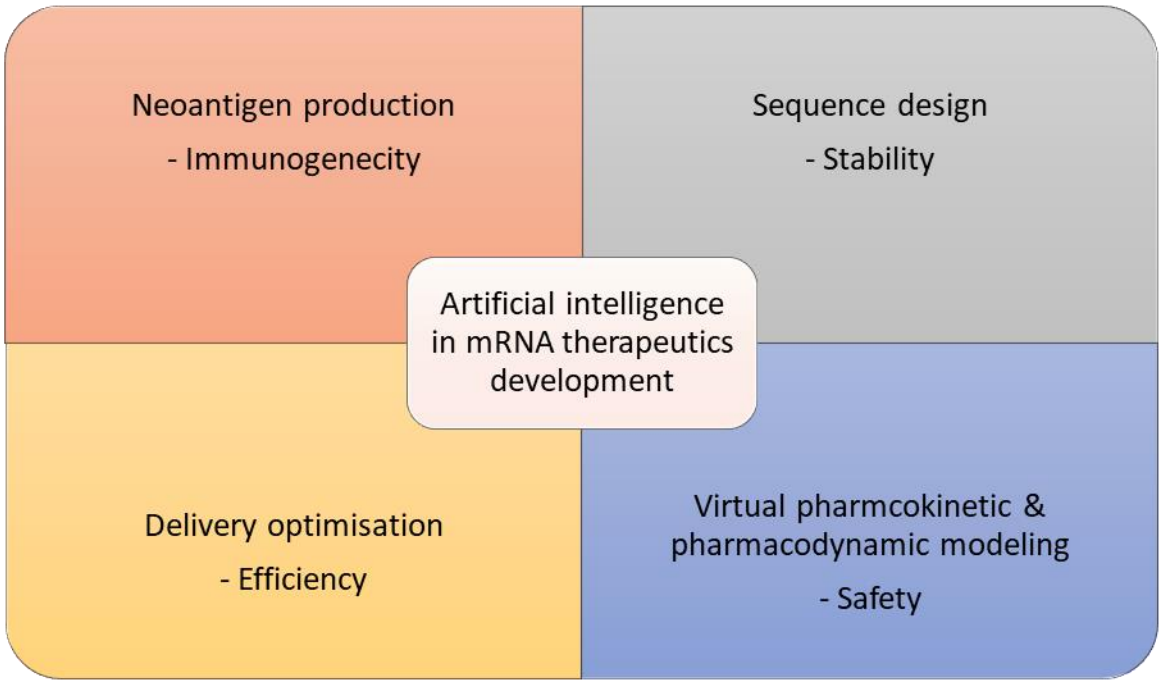
6. MRNA vaccines using LNP technology for lung cancer

Lung cancer is the most frequently diagnosed cancer and the primary cause of cancer-related fatalities. Non-small-cell lung cancer (NSCLC) is the predominant form of lung cancer, with around 40% of individuals diagnosed at stage IV metastatic disease. The treatment of lung cancer typically necessitates a combination of surgery, chemotherapy, or radiotherapy, depending on the type and stage of malignant tumors. Due to the shortcomings in early detection, lung cancer in the majority of patients is identified at an advanced stage, with distant metastasis or invasion of local tumors, making them unsuitable for surgical intervention. As the disease advances, the survival duration of patients with stage IV lung cancer slowly diminishes to 4 months. Consequently, it is vital to take action at an initial phase. Systemic cytotoxic therapy has emerged as the primary treatment for advanced NSCLC; however, the advantages of chemotherapy have plateaued, necessitating new treatment approaches. Systemic chemotherapy is the primary treatment for advanced lung cancer, intended to extend patients' survival duration and enhance their quality of life. The conventional first-line chemotherapy treatment for lung cancer consists of platinum-based medications (e.g., carboplatin and cisplatin). Platinum-based chemotherapy induces dose-limiting side effects such as intestinal injury, anaemia, nephrotoxicity, cardio toxicity, and peripheral neuropathy, along with symptoms like nausea, restlessness, and fatigue. Furthermore, the survival rates for classic chemotherapy regimens have leveled off, and the average survival duration for patients with molecular alterations addressed by new medications is roughly 2–3 years.

7. Development of mRNA Vaccines

The formulation of mRNA vaccines is essential for assessing the kinetics and level of antigen expression, along with the strength of the immune response. For instance, unmodified naked mRNA given intravenously was quickly degraded by rib nucleases and triggered the innate immune response; however, these issues can be addressed using suitable delivery systems and mRNA modifications. mRNA vaccines are provided through systemic or localized methods depending on the needs for antigen expression localization. The primary delivery methods for mRNA vaccines targeting infectious diseases are direct intramuscular (i.m.), intradermal (i.d.), or subcutaneous injection of in vitro transcribed mRNA, whereas intraperitoneal (i.p.) and intravenous (i.v.) methods are used for

systemic expression of relevant antigens, particularly in therapeutic settings. Several recent reports have demonstrated that diverse antigens can be expressed efficiently and elicit strong humoral and cellular immune responses following mRNA vaccination. Lipid nanoparticles (LNP) containing nucleoside-modified conventional mRNA that encodes firefly luciferase have been utilized to investigate how the administration route affects the kinetics of antigen expression. Intramuscular (i.m.) and intradermal (i.d.) injections resulted in optimal levels and duration of effect, with peak protein production occurring at 4 hours and localized maintenance lasting 8–10 days after injection, subject to the dose. Both i.m. and i.d. administration in Rhesus macaques using nucleoside modified conventional mRNA encoding influenza H10 encapsulated in LNP generated protective titers, but the response was quicker with i.d. administration compared to i.m. administration.



8. Advantages of mRNA vaccines

1) Facilitates the drug ability of intracellular, Tran's membrane, and secreted proteins.
2) Re-establishes gene expression without the danger of genomic integration.
3) Drug-like behaviour: capacity to repeat administration and modify dose/dosing schedule.
4) Endogenous post-transcriptional modifications enhance the likelihood of proper folding, glycosylation, and trafficking of the protein while reducing the chance of immunogenicity.
5) Slight modifications to the production method for several targets.
6) Quick progression from choosing target genes to selecting product candidates.

While several vaccines targeting parasitic infections in humans have been developed at the pre-clinical stage, and some are currently in early clinical trials, only the malaria vaccine has so far received licensure.A successful vaccine should enhance the immune response in a way that is stronger

than the body's natural innate and adaptive defenses.Most approved vaccines also create a memory immune response, which offers long-term protection against infection.In this discussion, we will examine the benefits and drawbacks of the mRNA vaccine development platform in this context.

9. Development of the COVID-19 mRNA vaccines

The two authorized COVID-19 mRNA vaccines, BNT162b2 and mRNA-1273, both include mRNAs that encode the SARS-CoV-2 spike (S) protein, a type I transmembrane glycoprotein composed of 1273 amino acids that determines the virus's infectivity. A shared characteristic is their possession of two amino acid substitutions, specifically K986P and V987P, in the peptide chain to enhance the stability of the S protein's prefusion conformation.112,172 Moreover, both utilize N1-methyl-pseudouridine in place of uridine as a substrate to reduce innate immune responses to mRNAs.

Nonetheless, the strategies for capping vary. Capping for BNT162b2 is achieved co-transcriptionally using the previously mentioned CleanCap cap analogues,84,173 whereas mRNA-1273 capping is accomplished through post-transcription reactions facilitated by the vaccinia capping enzyme and 2′ O-methyltransferase as previously noted.84,174 Additional modifications of the S antigen have also been examined. In a certain study, versions of the wild-type S antigen featuring two proline substitutions (2P), four additional proline substitutions (6P), removal of the furin cleavage site, and deletion of the endoplasmic reticulum retention signal were evaluated for their ability to trigger neutralizing antibodies

10. Previous worries regarding environmental distribution and "vaccine" categorization-

As stated, electric vehicles can significantly enhance the spread and expression of synthetic mRNA.Based on their natural properties, this process is not limited to transporting vaccine components within the bodies of vaccinated individuals but also extends to their release into the environment. The exact mechanisms intended by those who developed these vaccines are not fully known, but it is now clear that the possibility of spreading vaccine-related materials has been a serious concern for a long time. Pfizer, in its clinical protocol [6] for its mRNA-based COVID-19 vaccine, was particularly concerned about exposure through inhalation or skin contact, and such incidents were supposed to be reported to the company. Even as early as 2015, the FDA, in its 'Guidance for Industry' documents [80], expressed significant concerns about such a 'shedding' phenomenon—which has only recently come under scrutiny and 'fact-checking,' leading to widespread worries about the health effects on individuals who come into contact with vaccinated humans and animals, as well as the broader environment. In that guidance, the FDA defines shedding as the way a product is 'excreted or released from the patient's body.' This guidance was prepared before the introduction of mRNA vaccines but is still applicable to gene therapy products, which are defined as including substances 'that mediate their effects by transcription and/or translation of transferred genetic material.' It is important to note that this description aligns exactly with the intended mechanism of

mRNA vaccines. Additionally, Modern, in their official SEC filing in 2020 [79], clearly stated that 'mRNA is considered a gene therapy product by the FDA.' Similarly, Biotech founder UGu Sach earlier mentioned that 'one would expect the classification of an mRNA drug to be a biologic, gene therapy, or somatic cell therapy' [62], and this was acknowledged by Biotech in their official SEC filing.

11. MRNA Delivery via Nanoparticles

Nanomedicine is a field that brings together many different areas of study with the goal of making traditional medicines safer and more effective by using the special properties of nanoparticles.One key benefit is the ability to extend the time that drug molecules stay in the bloodstream, which is especially important because many drug molecules have low solubility and are not very stable.Poor pharmacokinetics and distribution of drugs can happen for several reasons, such as the hydrophobic nature of some drugs and the absence of a targeting system to deliver the treatment to the right location in the body.In addition, the body's natural immune system and organs like the kidneys and liver can quickly remove these drugs, reducing their time in the bloodstream and causing some of them to be destroyed or delivered to the wrong place.Using nanocarriers to prolong the time drugs remain in the blood can help improve their effectiveness while also reducing harm to healthy cells.By optimizing how drugs are absorbed and distributed in the body, nanodrugs are more likely to reach their intended target, leading to better bioavailability.Passive targeting depends on the structural features of nanoparticles, such as their size, shape, and charge, to help them accumulate at the right site and release their contents.For cancer treatments based on nanoparticles, longer circulation times are especially helpful because they can take advantage of the enhanced permeability and retention effect, which occurs due to the leaky blood vessels that are common in many tumors.

12. Mechanism of Immune Reaction Triggered by mRNA Vaccines

The immune response mechanism instigated by mRNA remains to be elucidated. The process of mRNA vaccine recognition by cellular sensors and the mechanism of sensor activation are still not clear. Intracellularly, two kinds of RNA sensors, endosome toll-like receptors (TLRs) and the RIG-I-like receptor family, have been identified. The former set is divided into TLR-3, TLR7, TLR8, and TLR9, which are localized in the endosomal compartment of professional immune surveillance cells, such as DCs, macrophages and monocytes. TLR3 recognizes dsRNA longer than 45 base pair as well as dsRNA resulting from single strand RNA (ssRNA) forming secondary structures or derived from viral replication intermediates. TLR7 and TLR8 are activated by RNAs rich in polyuridines, guanosines and/or uridines. TLR7 can bind both dsRNA and single-stranded RNA (ssRNA), whereas TLR8 recognizes ssRNA only. TLR7 activation can increase antigen presentation, promote cytokine secretion and stimulate B cell responses. The latter family, functioning as a pattern recognition receptor (PRR), includes RIG-I, MDA5, and LGP2. RIG-I preferentially recognize ssRNA and

dsRNA bearing a 5′triphosphate, and stimulate IFN production. The panhandle structure in viral genome segments was directly involved IFNinduction through RIG-I activation. MDA5 is another cytosolic RNA sensor that detects long dsRNA generated during RNA virus replication as well as RNA of synthetic origin, including poly I:C. Recognition by dsRNA induces the activation of IRF3 and NF-κB, subsequently leading to increased production of type I IFN. Sometimes, the elements of dsRNA recognized by PRR sensors can function as an adjuvant through the induction of IFN. mRNA vaccines can stimulate innate immunity through TLRs 3,7, and 8, RIG-I and MDA5

Once mRNA vaccines enter cells, they act as pathogen-associated molecular patterns (PAMPs) that are detected by the pattern recognition receptors (PRRs) of the host cell [125].These PRRs bind to specific molecules, which leads to the activation of type I interferon and NF-κB signaling pathways.These pathways are essential for initiating both innate and adaptive immune responses.

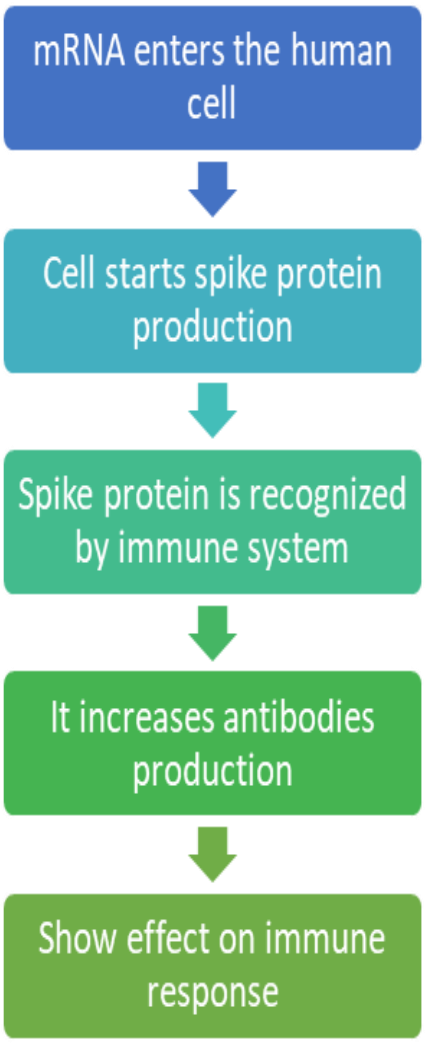
The most significant PRRs that identify foreign RNA are toll-like receptors (TLRs) found on endosomes and retinoic acid-inducible gene I-like receptors (RLRs) located in the cytoplasm.The TLR family includes TLR3, TLR7, and TLR8.TLR3 can recognize and attach to double-stranded RNA (dsRNA) that is longer than 45 base pairs, as well as single-stranded RNA (ssRNA) that has a structured shape or dsRNA produced during viral replication.This recognition helps control the IFN-I pathway and the release of cytokines and chemokines.

LNP-mRNA complexes are mostly kept at the injection site, such as the deltoid muscle, and are absorbed by nearby antigen-presenting cells, like dendritic cells, or by the surrounding muscle cells.Inside the cell, the LNP causes the cell membrane to fuse or, when the environment becomes acidic within an endosome, releases the mRNA into the cytoplasm.Then, the mRNA is used by ribosomes to make the target antigen protein.This process is important because it is the key difference between mRNA vaccines and traditional vaccines, as it imitates the way proteins are made during a natural viral infection.

The maturation of dendritic cells (DCs) is essential for the efficacy of mRNA-based vaccines. Typically, TLR7 is found in plasmacytoid dendritic cells (pDCs) and B cells in humans, while TLR8 is detected in conventional dendritic cells (cDCs), monocytes, and macrophages. cDCs represent the primary resident DC population in healthy human dermis and are marked by CD1c expression (also referred to as blood dendritic cell antigen-1 (BDCA-1)), whereas plasmacytoid DCs are located in the skin. The presence of TLR7 and TLR8 in various DC subsets and their locations across different organs could shed light on how immune effectiveness relates to the administration route and formulation of mRNA vaccines. The substitution of altered nucleotides in mRNA reduced the activation of PRRs by binding to mRNA, leading to a weakened innate immune response (153). mRNA vaccines stimulated both the specific humoral immune response through the translated antigen and the T cell response specific to the antigen. The mode of administration and the vaccine composition influence the maximum level of antigen expression, providing another method to adjust the immune response (94, 154, 155). Liang et al. demonstrated that the kinetics of cell infiltration was

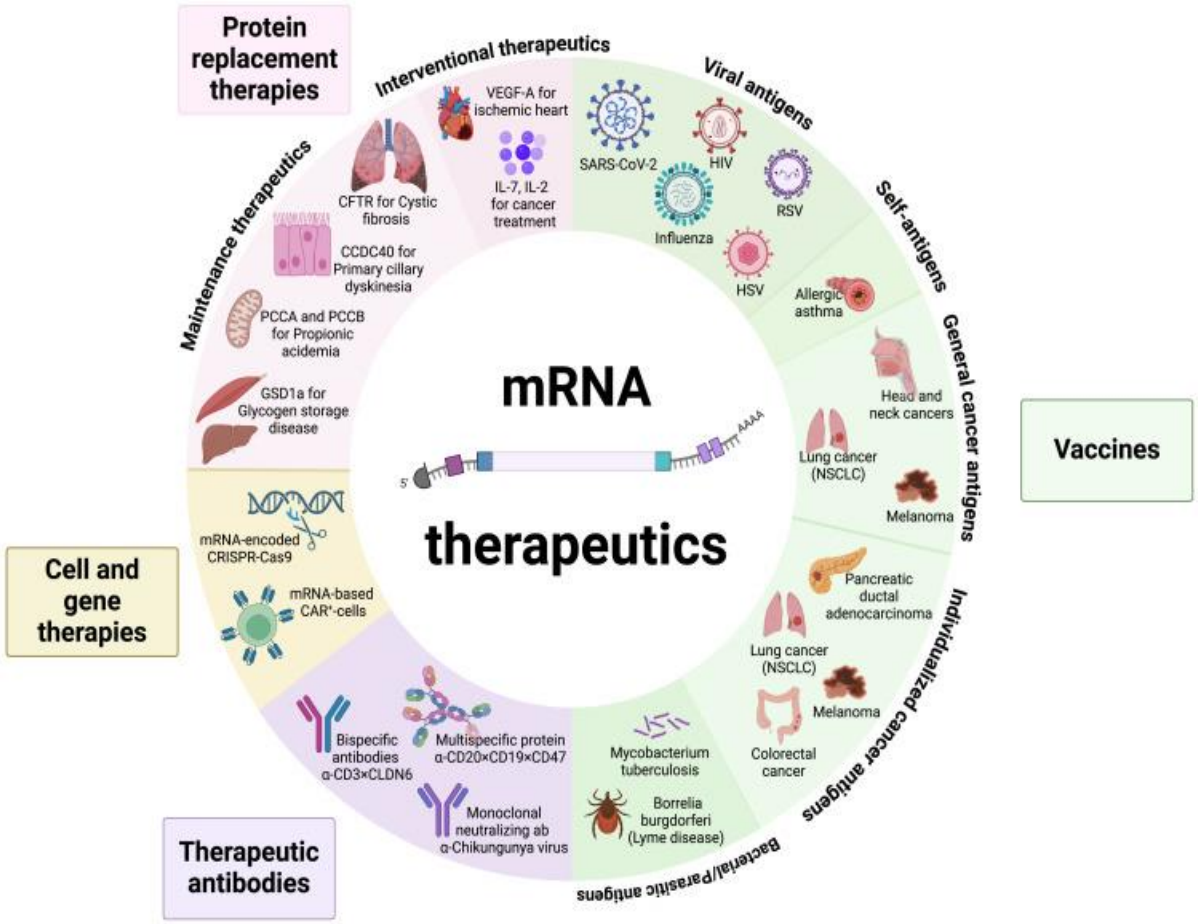
largely comparable between i.m. and i.d. administration in NHPs (156). The i.d. group displayed more vigorous initial reactions, likely due to the swift targeting, activation, and transportation of skin DCs to dLNs. Additionally, only skin monocytes and dendritic cells exhibited signs of antigen translation at day 9, suggesting sustained antigen presence following intradermal delivery, and validating the extended expression of mRNA-encoded antigen noted in mice (94).

A clearer explanation of the events that lead to mRNA translation and immune activation will assist in designing mRNA vaccines to achieve the appropriate balance of type I IFN induction, enhancing vaccine efficacy.



COVID-19 messenger mRNA vaccines.

13. Clinical advancement of mRNA treatments

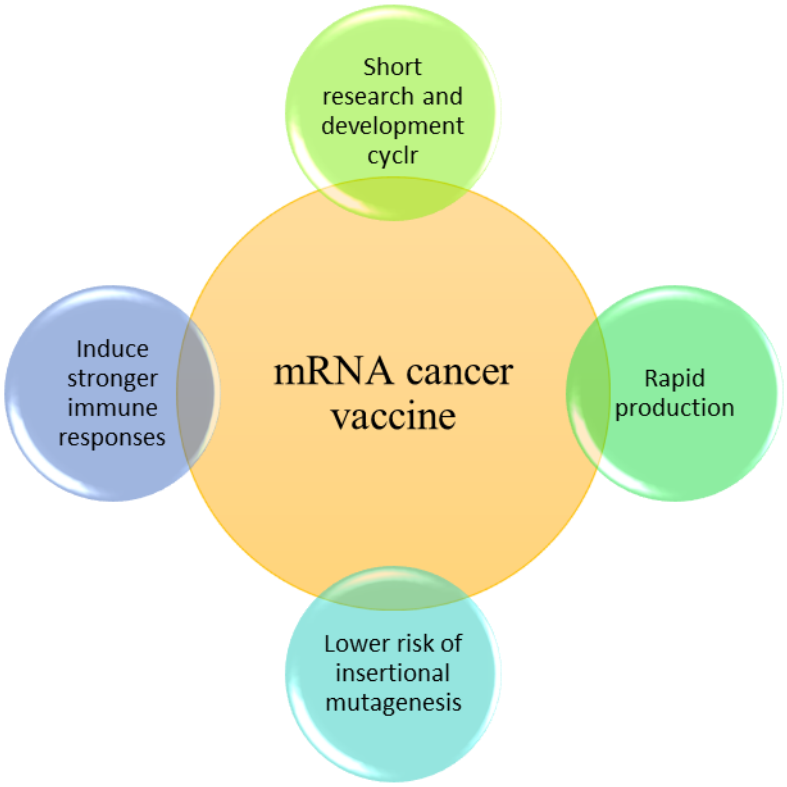


MRNA therapeutics are now in the spotlight, ready to take on a more significant role in contemporary medicine. As mentioned earlier, mRNA serves as an effective agent that allows patients' cells to generate any protein considered therapeutically advantageous. This flexibility enables its use in nearly all disease contexts where the administration of therapeutic proteins may be advantageous. This review examines mRNA therapeutics in development that have reached at least phase 1 clinical trials or are in later phases of preclinical assessment. The versatility of mRNA technology enables the creation of various drug types, such as vaccines aimed at viral, bacterial, cancer-specific (both general and individualized), and self-antigens; therapeutic antibodies; and protein replacement therapies for maintenance and intervention treatments. Moreover, mRNA can be utilized in gene modification and cell-derived therapies (Figure 1). We examine the mRNA types presently utilized in clinical settings, including linear mRNA, acting as a standard, non-amplifying transcript; self-replicating mRNA, which incorporates replicase machinery to boost protein expression; and circular mRNA.

14. Applications of mRNA vaccines

Therapies based on mRNA are anticipated to treat numerous diseases that do not respond to existing treatments, including infectious illnesses, metabolic genetic disorders, cancer, cardiovascular issues, cerebrovascular problems, and more [164]. mRNA medications can provide added benefits of high

efficacy with minimal side effects and simplified production. Consequently, mRNA vaccines have demonstrated their safety and efficacy as a method to reduce the transmission of COVID-19 [34]. The initial mRNA vaccine to obtain emergency use authorization was developed by BNT/Pfizer (BNT162b2), and its approval was swiftly succeeded by that of the Moderna vaccine (mRNA-1273).



Applications of mRNA cancer vaccine

As knowledge about the roles of natural and synthetic circular RNAs (circRNAs) grows, there is increasing interest in using circRNAs for therapeutic and vaccine purposes.For instance, introducing external circRNAs has been shown to effectively trigger strong innate immune responses against viral infections [63].Importantly, circRNAs have been investigated as potential vaccines to prevent coronavirus disease 2019 (COVID-19).This involves designing circRNAs that encode the receptor-binding domain (RBD) of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which helps generate a strong RBD-specific immune reaction in the body [25].Additionally, synthetic circRNAs have been tested for their ability to produce neutralizing antibodies against SARS-CoV-2 pseudoviruses, offering a ”protein replacement” strategy for treating COVID-19.

15. CONCLUSION

mRNA vaccines have emerged as a focal point in disease prevention and therapy, taking a leading role in both preclinical and clinical studies, particularly in infectious diseases and cancers.141 However, apart from the anti-COVID-19 mRNA vaccine, only a limited number have received approval for disease treatment so far. Various challenges remain unaddressed that could restrict the

use of mRNA vaccines. Finding a balance between maximizing antigen production and providing sufficient adjuvant effects presents a considerable challenge. The adjuvant properties of mRNA vaccines enhance both innate and adaptive immunity, yet an overactive innate immune response can hinder mRNA translation.8,246 Strategies such as 5′ capping, nucleoside modification, poly(A) tail modification, and HPLC purification are employed to mitigate innate immunity.17,247,248 Further exploration of the relationship between the delivery carrier mRNA and the innate immune system is essential for establishing an optimal balance. Another obstacle is the mass production of mRNA. Due to the absence of a continuous manufacturing process, synthesis, purification, and formulation need to occur in separate facilities across three states in the USA, significantly hindering the swift production of mRNA vaccines. For example, producing millions of doses of BNT162b2 requires 60 days, which is insufficient to meet the vaccination requirements of 6 billion individuals globally.

This review article emphasized the crucial impact of mRNA vaccines in transforming the prevention and treatment of infectious diseases. Conventional vaccine methods face constraints in scalability, development speed, and adaptability to new pathogens, whereas mRNA vaccines provide a flexible and quick solution for focused vaccine creation. The modular design of mRNA vaccines permits straightforward modification for various pathogens, and their quick manufacturing capabilities offer versatility in addressing any emerging infectious diseases. Nonetheless, the effective transport of mRNA molecules presents a challenge, which was tackled by employing nanoparticles as delivery vehicles. LNPs have become the foremost category of nanoparticles for delivering mRNA vaccines, offering protection, effective cellular uptake, and regulated release of the mRNA payloads.

In conclusion, mRNA vaccines present remarkable potential for the future of infectious diseases and cancer treatment. Their adaptability, flexibility, and quick production abilities make them essential assets in disease prevention and therapeutic treatments. Additional studies are required to investigate their complete capabilities, tackle issues, and enhance their application in various disease scenarios. Going forward, it is suggested that upcoming studies emphasize enhancing vaccine design, delivery methods, and production processes. Grasping the long-term safety and resilience of immune responses produced by mRNA vaccines is crucial. Moreover, investigating the integration of mRNA vaccines with various immunotherapeutic methods could further improve their effectiveness. Ongoing studies and partnerships in mRNA vaccines will open doors to groundbreaking solutions for disease prevention and treatment.

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