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Review Article

mRNA-based cancer vaccines: A new frontier in personalized immunotherapy

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ABSTRACT

The advancement of mRNA technology has rejuvenated the cancer treatment immunotherapy field by providing a flexible and scalable platform to generate tumor-associated or patient-specific neoantigens, which induces strong cytotoxic and helper T-cell outcomes and also immunologically stimulates innate immunity in the body at the same time. In contrast to conventional vaccines, mRNA preparations are non-integrative, safe, and scalable, allowing personalization of mutational landscape-based vaccines much faster due to the unique mutations of tumors in individuals. Early clinical trials in melanoma, breast, glioblastoma, and pancreatic cancer have revealed encouraging immunogenicity results, especially when used along with checkpoint inhibitors or other complementary therapies. The recent news of discovering the mRNA cancer vaccine, Enteromix, in Russia, also points to the potential of the translation and the global trend of this technology, which is both effective in treatment and accessible in clinical practice. Although the issues such as heterogeneity of the tumors, antigen escape, delivery efficiency, and manufacturing logistics are present, the development of artificial intelligence, multi-omics integration, and next-generation delivery systems will address these challenges. This review gives an overview of the concepts and principles, types, delivery mechanisms, clinical applications, and future perspective of mRNA-based cancer vaccines with a focus to its revolutionary contribution to personalized oncology and the overall next-generation immunotherapy.

1. Introduction

The problem of cancer is one of the most significant health issues in the entire world, as the rates of its occurrence and death are rising, albeit with improved methods of treatment using surgery, chemotherapy, radiotherapy, and targeted therapy. In the last twenty years, with the development of immunotherapy, the treatment paradigm in subgroups of patients has changed, providing long-term remedies. The objective of immunotherapies involving checkpoint blockade as well as adoptive cell therapies and cancer vaccine methods is to instruct the host immune system to selectively detect and kill malignant cells [1]. Immune checkpoint inhibitors (ICIs) targeting CTLA-4 and PD-1/PD-L1 pathways have demonstrated significant survival benefits in melanoma and non-small cell lung cancer (NSCLC), as evidenced by several pivotal clinical trials [2,3]. Likewise, chimeric antigen receptor (CAR)-T cell therapy has achieved remarkable remission rates in hematological malignancies, particularly B-cell acute lymphoblastic leukemia and large B-cell lymphoma [4,5]. However, these approaches are not universally effective, and primary or acquired resistance remains a clinical challenge, underscoring the need for complementary immunotherapeutic strategies. Among emerging modalities, therapeutic cancer vaccines aim to stimulate tumor-specific immune responses by presenting tumor-associated antigens (TAAs), which are self-proteins aberrantly or overexpressed in malignant cells, compared to normal tissues, making

Abbreviations: AI, artificial intelligence; APC, antigen-presenting cell; CAR, chimeric antigen receptor; CTL, cytotoxic T lymphocyte; CTLA-4, cytotoxic T-lymphocyte–associated antigen 4; DC, dendritic cell; ICIs, immune checkpoint inhibitors; LNP, lipid nanoparticle; MHC, major histocompatibility complex; mRNA, messenger RNA; NSCLC, non-small cell lung cancer; PD-1, programmed death-1; PD-L1, programmed death ligand-1; saRNA, self-amplifying RNA; taRNA, trans-amplifying RNA; TAA, tumor-associated antigen; TLR, toll-like receptor; TME, tumor microenvironment; TSNAs, tumor-specific neoantigens; UTR, untranslated region.

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them recognizable targets for immune intervention, or in contrast tumor-specific neoantigens (TSNAs), which arise from somatic mutations unique to cancer cells and are absent in normal tissues, enabling more precise immune targeting, thereby enhancing cytotoxic T-cell activation [6,7]. While early peptide- and protein-based vaccines demonstrated limited efficacy, nucleic acid-based platforms, particularly messenger RNA (mRNA) have introduced a flexible and immunologically potent strategy for cancer immunotherapy [8].

The advent of mRNA-based vaccines as a validated platform in the COVID-19 pandemic is one of the turning points in the modern medicine. The technical and physical instability of mRNA and the technical difficulty of delivery have generally remained barriers to the field over decades; however, these obstacles were surmounted by chemical modification of nucleosides, optimization of untranslated regions (UTRs), and the creation of lipid nanoparticles (LNPs) delivery systems [9]. Their scalability and safety, as evidenced by the rapid success of mRNA vaccines in the prevention of SARS-CoV-2 infection, not only accelerate their adoption in oncology, but also enabled them to be used in other areas. In comparison to DNA vaccines, mRNA requires no nuclear entry or is not prone to genomic insertion, which provide temporary expression of antigens encoded within it with high safety. Moreover, mRNA vaccines have an innate adjuvate properties of innate immune sensors, and at the same time, they allow elicitation of robust CD8+ cytotoxic T-cell and CD4+ helper T-cell responses [10].

The case of applying mRNA technology to oncology is convincing. Cancer is genetically heterogeneous disease, and every tumor has its own repertoire of mutations which lead to neoantigens. The identification of patient-specific neoantigens and the production of individualized mRNA vaccines encoding patient-specific neoantigens is now possible in a relatively quick manner with the aid of next-generation sequencing and bioinformatics prediction tools [11]. This technology offers the advantage of offering the opportunity to incorporate several epitopes into one vaccine to reduce chances of immune evasion. mRNA vaccines can also be created in a modular manner with high speed, which reinforces their application in personalized medicine whereby the treatment should be centered to match the changing genetic landscape of individual tumors. Notably, mRNA vaccines also have a synergistic effect with other immunotherapies; stimulating the tumor-specific T cells promotes checkpoint blockade therapies that stimulate T-cell activity in the tumor microenvironment (TME) [12].

In this review, we assess the current position of mRNA-based cancer vaccines that start with the basic design and action mechanism, the main types and delivery platforms currently under investigation. We highlight the progress that has been achieved in clinical trials in different forms of cancer; the constraints preventing their use in the mainstream, and what are the new methods that are being explored to overcome the constraints. So that we are finally brought to consider the future of the mRNA cancer vaccines in the larger picture of personalized oncology to which they can one day be incorporated alongside multi-omics data, artificial intelligence (AI), and new combinations therapies to become a buttress of cancer treatment [13].

2. Principles of mRNA cancer vaccines

The concept of an mRNA-based cancer vaccine is connected to the ability to encode tumor-specific antigens and release them to the body in the form of an effective and long-term immune response. Unlike protein or peptide vaccines, which are generated on the basis of availing the antigens directly, mRNA vaccines avail the genetic template, which grants the host cells the authority to create the target antigens directly. This is not only to imitate the natural process of virus infection but also to ensure that the innate and adaptive branches of the immune system interact effectively [14]. An mRNA vaccine is physiologically composed of a designed mRNA strand that is surrounded by a device of delivery. The mRNA sequence will encode TAAs or hopefully, TSNAs due to specific mutations in the cancer genome. To have an ideal stability and translation efficiency, the mRNA is terminated with a structure at the 5-end comprising of an optimized UTRs and poly(A) tail which can bear chemically modified nucleosides to reduce recognition by enzymes that break down RNA. However, naked mRNA exists in this state and needs to be readily disintegrated by extracellular ribonucleases [15]. To overcome this, the mRNA is entrapped and encased in highly developed delivery methods such as LNPs. These carriers are not only perceived to stabilize the antigen but also increase the possibilities of the antigen being taken up by the antigen presenting cells (APCs), in this case, the dendritic cells (DCs), and its uptake is a vital stage in the process of conducting antitumor immunity. Other methods of delivery, either through the use of polymer-based carriers or direct intra-nodal electroporation are also explored, however the most clinically proven platform is LNPs [16].

The mechanism of action is highly complicated with an immunologically regulated process that occurs after delivery. The mRNA cargo is then released into the cytoplasm of host cells, which then translates the cargo into tumor antigen proteins with the cellular ribosomal machinery. These freshly produced antigens are in turn degraded by the proteasome and oriented on the cell surface by way of major histocompatibility complex (MHC) molecules [17]. Specifically, the antigenic peptides get loaded in the MHC class I molecules being bound by the cytotoxic CD8+ T lymphocytes which leads to the activation of potent effector cells that can directly kill the tumor cells that express the same antigens. In the meantime, exogenous antigen presentation pathways permit the possibility of peptides appearing in class II of the MHC molecules thereby leading the activation of CD4+ helper T cells [18]. These facilitating cells also play a major role, as they harbor the cytokine support and co-stimulatory signals needed to sustain cytotoxic T-cell activity and activate production of long-term immunological memory. Such dual interaction of CD8+ and CD4+ T cells is what makes mRNA vaccines a highly promising immunotherapy platform.

Contrary to other more traditional protein or peptide-based vaccines, which uses exogenous directed antigens to activate the immune response, the mRNA vaccines allow the intracellular *in-vivo* production of antigens directly within the APCs, which is more closely associated with endogenous viral infection. Following cellular uptake, primarily by DCs, the delivered mRNA is released into the cytoplasm and translated by host ribosomes into TAAs or TSNAs. This intracellular production helps to undergo efficient processing and presentation in MHC class I pathways thereby enhancing a strong CD8+ cytotoxic T-cell responses. Simultaneously, the apoptotic or exercised antigen fragments can be recognized by adjacent APCs, marking it off and activating cross-presentation and CD4+ helper T cells *via* MHC class II pathway amplifications [19].

The highly exclusive aspect of mRNA vaccines is their innate immunostimulatory ability. Pattern-recognition receptors (PRRs) which are recognized as proteins serve to detect the presence of single-stranded RNA that include: Toll-like receptors (TLR3, TLR7, and TLR8) and cytosolic receptors such as RIG-I and MDA5. Type-I interferon and pro-inflammatory cytokine generation or stimulation of DC maturation and co-stimulatory molecule upregulation occurs with ligation to these pathways (Fig. 1). Consequently, mRNA vaccines can function both as an antigen source and a self-adjuvant, reducing the need for external adjuvants used in many conventional vaccine platforms. Furthermore, the non-integrating, cytoplasmic nature of mRNA eliminates genomic integration risks associated with DNA-based approaches, enhancing safety. Together all these properties such as, cytoplasmic translation, effective MHC class I presentation, intrinsic innate immune activation, and modular antigen design, make mRNA vaccines mechanistically better than peptide, protein, and viral vectors platforms and justify their use in personalized cancer immunotherapy [20].

mRNA cancer vaccines have the potential to eliminate tumors while also reducing recurrence by inducing both immediate effector responses and durable immunological memory [21]. In addition, the temporary expression of mRNA-encoded antigen makes it safe, as the encoded

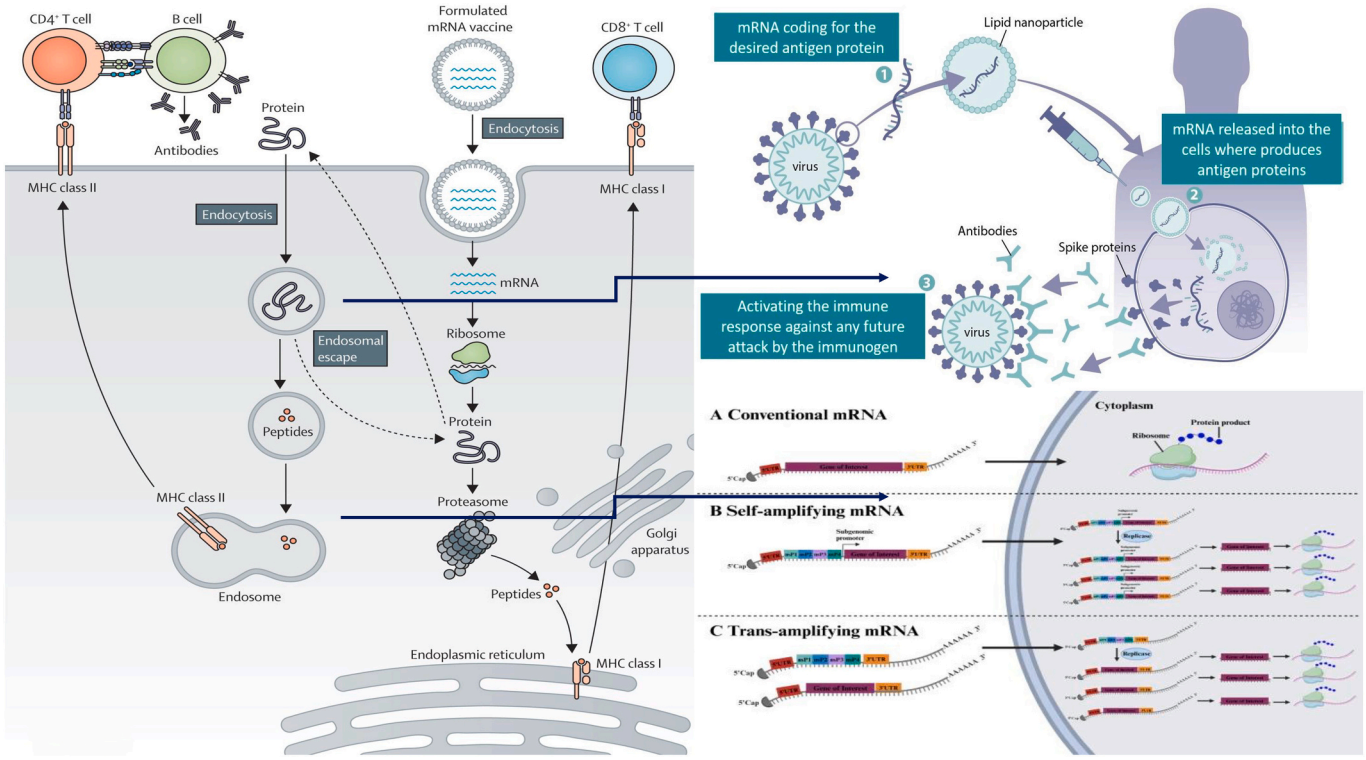

Fig. 1. Mechanism of action and structural classes of mRNA cancer vaccines.
Antigen presentation: mRNA can be translated into TAAs that are then processed and displayed on MHC class I and II molecules after uptake by APCs. This dual activation stimulates cytotoxic CD8+ T cells and helper CD4+ T cells, leading to both effector and long-term immunity. Delivery principle: LNPs-formulated mRNA protects transcripts against degradation, facilitates endosomal escape, and enables cytoplasmic release, thereby promoting efficient antigen expression and activation of both innate and adaptive immunity. Structural formats: Non-replicating mRNA encodes only the target antigen; self-saRNA includes viral replicase elements to enhance antigen production at lower doses; and trans-amplifying mRNA (taRNA) separates replicase and antigen into distinct transcripts, enabling modular and scalable vaccine design.

proteins are expressed only to a limited extent, since the mRNA is degraded naturally, thus risks of long-term off-target effects are minimized. Nevertheless, this natural activation should be strictly adjusted because, with its excessive stimulation, inflammation can occur, or the expression of antigens can be compromised [22].

Fundamentally, the concept of mRNA-based cancer vaccine is beautifully simple but biologically potent; offer the body with a genetic template of molecular instructions to temporarily express cancer-specific antigens, enable the immune system to recognize them in the right setting, and to generate a custom-made immune response that can destroy malignant cells. This mRNA programmability and modularity make it exceedingly customizable, where a vaccine can encode the actual neoantigens present in a cancerous tumor of a patient to allow personalized immunotherapy to be obtained in cancer treatment [23,24].

3. Classes of mRNA-based cancer vaccines

The mRNA cancer vaccines are broadly categorized into two formats as non-replicating mRNA vaccines and self-amplifying mRNA (saRNA) vaccines. The two relate to each other in the principle of guiding host cells to produce tumor antigens but are different in design, complexity and immunological strength. This is critical to knowing the clinical uses and how they can be helpful in oncology. Understanding these distinctions is therefore important for escalating their clinical applications and potential advantages in oncology [25–27].

The simplest and most common type of vaccines are non-replicating mRNA vaccines. They are made up of a linear strand of mRNA that only codes the antigen of interest which is surrounded by structural elements including a 5-cap end, optimized UTRs, and poly(A) tail. After being transferred to host cells, this mRNA is translated into tumor antigens which are processed and presented to the immune system. Since they have no viral replication machinery, non-replicating mRNA vaccines are naturally safe, and the associated expression of antigens naturally deteriorates as the mRNA decays. They are relatively simple and quick to manufacture by their simple design, which has proven them to be particularly beneficial with the high speed with which mRNA vaccines can be deployed in the context of infectious diseases. Their greatest limitation, however, is that their duration and degree of antigen expression is rather short and could necessitate higher doses or recurrent injections in order to produce a strong immune response against tumors [26,27].

The saRNA vaccines, on the other hand, have designed to amplify antigen production and prolong it. They are vaccines that are usually based on modified alphavirus genomes, whereby the viral genes that encode structural proteins are deleted and the tumor antigen sequence inserted in their place, although the viral replicas complex is retained. After entry into host cells, the replicas machinery increases the mRNA, which allows repeats of transcription, thus producing significantly higher amounts of antigen than non-replicating constructs [28]. The implication of such amplification is that the powerful immune reactions to the case of saRNA vaccines can be achieved by low doses, which will create fewer manufacturing challenges and, possibly, improve access. Moreover, long-term generation of antigens is more effective to sensitize cytotoxic T cells and develop memory, which are also necessary to control tumors in the long term. Nevertheless, the additional complexity of saRNA is problematic in terms of the molecular size, delivery efficacy, and innate immune activation that may be higher, in which case one needs to strike a balance between that to achieve neither excessive inflammation nor lethality [29].

The use of both the non-replicating and self-amplifying forms of formats involves the differently constructed cancer vaccines. Non-replicating mRNA vaccines are straightforward, safe and have been shown to be clinically feasible, making them well adapted to the rapid personalization especially in neoantigen vaccines strategies targeted to a specific patient. On the other hand, self-amplifying vaccines provide a platform upon which dose-sparing and enhanced immunogenicity is of high-priority and that can find increased use in larger-scale and off-the-shelf cancer vaccine indications. This kind of comparative clinical trials and preclinical studies is being done and there may be a complementary opportunity of the two forms in the active field of mRNA-based cancer immunotherapy [30].

4. Advantages over traditional cancer vaccines

The *in-vivo* antitumor immunity inducers in conventional cancer vaccines include protein, peptide, or DC-based formulations. These platforms may possess conceptual merits, however, tend to have the negative response of low immunogenicity, length of production, and irregular clinical response, which can be antidote by mRNA-based cancer vaccines with predominant advantages, and hence, forms a revolutionary platform in cancer therapy.

The first major advantage of mRNA vaccines is their capacity for rapid personalization and flexible antigen design. Once the genetic sequence of a tumor and the abnormality that it carries is established, bioinformatics can be applied to forecast immunogenic neoantigens, and even mRNA constructs can be created within weeks [31]. This speed is highly favorable in the area of oncology where there is the likelihood of rapid growth of tumors and time is of importance in order to take a therapeutic measure. Unlike peptide vaccines, which require the complex production of chemical compounds and validation of each peptide, mRNA allows the encoding of multiple epitopes in the same construct to represent tumor heterogeneity as well as reduce the chances of immune evasion. This customization is possible not only because of this modularity, which is allowing customized cancer vaccines, but is progressively becoming more viable every day [32].

Another important advantage is their favorable safety profile and absence of genomic integration. mRNA does not enter the nucleus (as required by other forms of DNA-based vaccines) and therefore there is no hypothetical danger of mRNA changing host DNA and will be naturally degraded when protein translation is done. This is a temporary expression profile which mitigates safety concerns of the long-term profile and makes the technology suitable to participate in repeated dosage. Clinicians and patients can therefore have no hesitation to proceed with using mRNA cancer vaccines without losing the risk that the risk of insertional mutagenesis or irreversible genetic modification is extremely low [33].

The other remarkable advantage of mRNA vaccine platforms is that it can be optimized and reiteratively designed very quick. Some of the modifications of sequences, optimization of codons as well as modification of UTRs can greatly increase antigen expression, stability and increase translational efficiency [34]. Additionally, delivery mechanism complications bring about efficient cellular uptake and antigenic delivery to APCs. These technological advancements enable the ongoing enhancement of vaccine performance without making any changes to the underlying manufacturing platform [34,35].

Lastly, the technology of manufacturing mRNA vaccines on a platform is a significant strength of the technology. Under this strategy, the basic production process that involves *in vitro* transcription, purification, and formulation remains consistent, and the only element that requires alteration with diverse vaccine antigens is the RNA coded antigens sequence. This modular architecture enables rapid adaptation to newly identified TAAs or patient-specific neoantigens without requiring major changes in the manufacturing process. As a result, mRNA vaccines can be designed and produced more efficiently than many conventional vaccine formats that require redevelopment of protein antigens or viral vectors [36].

The platform nature of mRNA technology therefore facilitates scalable production and supports the rapid development of personalized cancer vaccines. The effectiveness of this platform-based strategy was clearly demonstrated during the COVID-19 pandemic, when mRNA vaccines were developed, manufactured, and distributed globally within an unprecedented timeframe. The same scalable production principles can be applied in oncology, enabling both the rapid generation of individualized vaccines targeting patient-specific neoantigens and the large-scale manufacturing of vaccines directed against shared tumor antigens [36,37].

Together, these advantages prove that why mRNA vaccines are an insurgency in cancer immunotherapy. They offer the speed and flexibility required to personalized medicine, the ability to take multiple doses that are needed to overcome tumor tolerance, the desired level of immunological strength and even scalability in manufacturing required to reach patients in every corner of the globe. Not only do these properties distinguish mRNA vaccines against their classical counterparts, however, these properties also warrant the present-day tidal shift of momentum toward their clinical use in the field of oncology [38]. A comparative overview of traditional vaccine strategies and mRNA-based cancer vaccines is provided in (Table 1), highlighting their distinct features, advantages, and limitations.

5. Delivery platforms

The effectiveness of mRNA cancer vaccines is not only dependent on the sequence of the coded antigens, but it is also important that the mRNA be transferred into the host cells in an efficient manner. Unprotected mRNA is unstable in nature and may easily be destroyed by extracellular RNases. In addition, induction of potent cytotoxic and helper T-cell responses requires efficient receptors of APCs particularly, DCs. To avoid these issues, several advanced delivery services have been created, and each of them has its own benefits and is taken into consideration [39].

The most commonly used and clinically advanced system of delivering mRNA vaccines is LNPs. These nanoparticles enclose the mRNA, which has been in the protection of lipid bilayer, where it is also not subjected to enzymatic breakdown and its uptake by the cells occurs *via* endocytosis. LNPs include mainly ionizable lipids, phospholipids,

Table 1
Comparative features of traditional *vs.* mRNA-based cancer vaccines.

Feature	Traditional Cancer Vaccines (Peptide/ Protein, DC-based)	mRNA-Based Cancer Vaccines	References
Antigen Source	Pre-synthesized peptides, proteins, or loaded DCs	*In vivo* expression of tumor antigens *via* delivered mRNA	7–9,13,15
Personalization	Limited (common TAAs)	High (patient-specific neoantigens)	11,12,31
Immune Activation	Often weak, needs adjuvants	Strong CD8+ and CD4+ T cell responses, innate activation *via* TLRs	10,17,21
Safety	Risk of tolerance, limited durability	Non-integrative, transient expression, low risk of genomic insertion	9,33
Scalability	Complex, time-consuming	Rapid, modular, scalable manufacturing	35–37
Durability of Response	Often transient	Induces immune memory, reduced recurrence risk	18,23,24
Clinical Limitation	Low immunogenicity, long preparation	Stability, delivery efficiency, tumor heterogeneity	65–69

cholesterol, and PEG-lipid conjugates, which improve their stability, endosomal escape and circulation duration. Once being internalized, LNPs facilitate the release of the mRNA into cytoplasm, which is then translated to tumor antigens [40]. The safety and efficacy of LNPs as a delivery system have been confirmed by the clinical success of mRNA COVID-19 vaccines, and current cancer vaccine clinical trials often employ LNP-formulated mRNA to assure strong immune response. Another potential method is polymeric carriers. Complexes with mRNA can be formed by polyethyleneimine (PEI), poly (lactic-*co*-glycolic acid) (PLGA), and dendrimers due to electrostatic interactions, which prevent degradation of the mRNA and allows it to be taken up by cells [41,42].

Certain polymeric systems have the added benefit of controlled release, which allows long-term expression of antigens and possibly more powerful immune responses. Although polymer-based delivery has shown promising preclinical outcomes, this technology has not yet been translated to the clinic as effectively as LNPs, mainly because of the concerns of biocompatibility, toxicity and less reliable scalability of manufacturing [43,44]. Other delivery strategies such as electroporation and *ex-vivo* DC loading can also be employed especially in case of highly personalized cancer vaccines (Fig. 2). Under these methods, the mRNA is transferred into DCs within the extracellular space of the patient through temporary pulse of electric shock, which also improves an increase in cell membrane permeability. The loaded DCs are inoculated into the patient where they present tumor antigens to the T cells causing specific immune responses. This technique allows changing antigen delivery and cellular stimulation finely, although it is tedious and costly and cannot be scaled to nanoparticle-based technologies [45,46]. The future of mRNA vaccines is yet to be set and emerging strategies in its delivery are currently under use. These might include hybrid lipid-polymer nanoparticles, targeted nanoparticles with surface ligands that presently target the APCs and biodegradable nanomaterials, which release mRNA in a controlled manner in lymphoid tissues. Single systems are rated not only on the efficiency of delivery, but also in addition to the possibility of finding a balance between immunogenicity and tolerability, minimizing the off-target effect, and facilitating clinical translation in large quantities [47,48]. The major classes of mRNA cancer vaccines, their delivery platforms, advantages, and current clinical relevance are summarized in (Table 2).

5.1. *Comparative analysis of mRNA delivery platforms*

Though the individual delivery platforms have proven its efficiency in different aspects, their impact on mRNA vaccine efficacy is directed by several interrelated determinants. First, the stability of mRNA and its resistance to degradation by RNase is essential to maintain the capacity of translation. LNPs provide superior encapsulation efficiency and

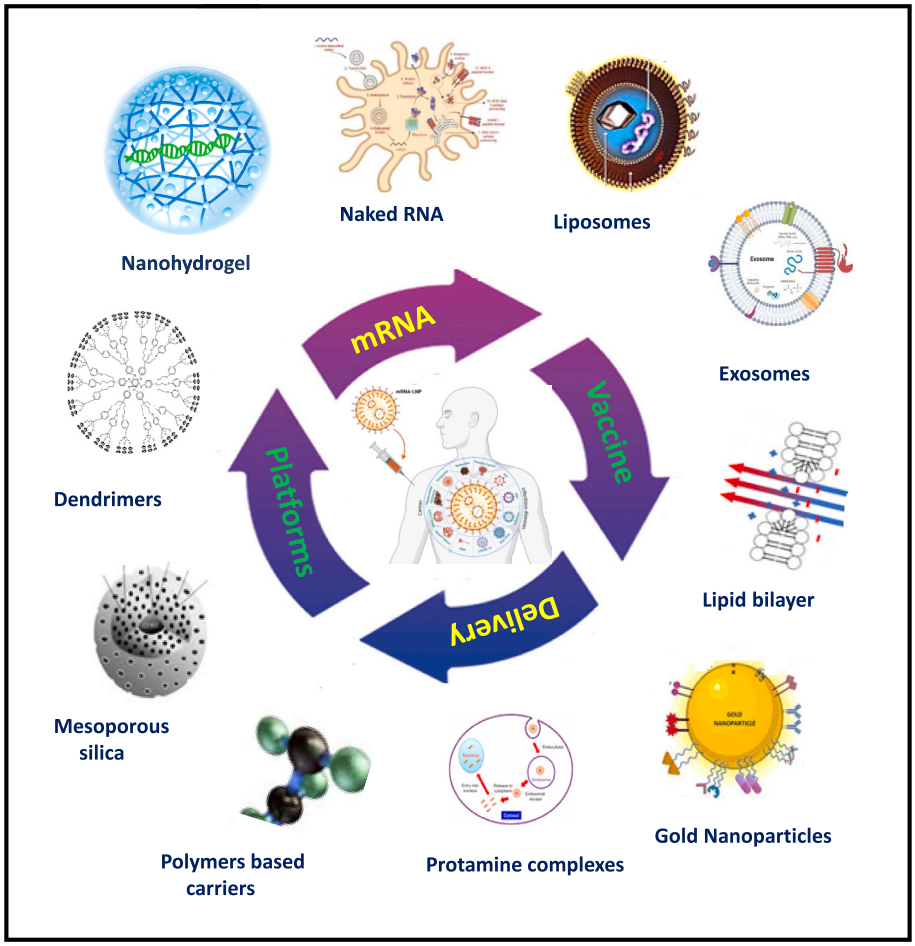

Fig. 2. Delivery platforms for mRNA cancer vaccines.
Different modes of delivery system that are designed to counter the natural instability of mRNA and to achieve high antigen expression. The most clinically tested and widely used approach is LNPs, which protect mRNA against degradation, facilitate endosomal escape, and enable efficient immune stimulation. Other methods include polymer-based carriers and protamine complexes, which stabilize transcripts and allow modulation of immune responses, as well as viral vector–based systems that provide high transfection efficiency but may raise safety concerns. *Ex-vivo* DCs loading represents a highly personalized strategy in which APCs are directly loaded with mRNA; however, this approach remains difficult to scale. The integration of these delivery strategies may collectively contribute to more stable, efficient, and clinically usable mRNA cancer vaccines.

Table 2
Classes, delivery platforms, mechanisms and key characteristics of mRNA-based cancer vaccines.

Vaccine Type / Platform	Mechanism	Advantages	Limitations	Clinical Relevance	References
Non-replicating mRNA	Encodes tumor antigen only; direct translation	Simple, rapid production, safe	Short antigen expression, may need boosters	Used in many early-phase trials	23–26
saRNA	Retains viral replicase to amplify mRNA	Prolonged antigen expression, lower dose needed	Larger molecular size, innate overactivation risk	Promising in dose-sparing cancer trials	27–29
LNPs	Protect mRNA, aid endosomal escape	Clinically validated, scalable	Cold chain needed, off-target uptake	Backbone of current vaccine trials	40
Polymeric Carriers (PLGA, PEI, dendrimers)	Electrostatic mRNA binding, controlled release	Sustained antigen release	Toxicity, less clinical validation	Preclinical only	41–44
Electroporation / *ex vivo* DC loading	Direct transfection of DCs	Highly personalized, precise antigen loading	Costly, labor-intensive	Investigational in personalized vaccines	45,46
Hybrid Nanoparticles & Future Systems	Lipid–polymer hybrids, biodegradable implants	Targeted, controlled, long-term release	Still experimental	Next-gen delivery platforms	47,78,79

systemic stability, whereas polymeric systems vary depending on charge density and formulation characteristics.

Second, maximum uptake of cells and minimal endosomal escape capacity are directly related to cytoplasmic mRNA availability. Ionizable LNPs have been shown to improve endosomal destabilization in acidic environments leading to efficient antigen expression. Polymeric carriers and electroporation-based methods, on the contrary, are based on other mechanisms and are characterized by changing intracellular release efficacy.

Third, immunological stimulatory capabilities of the delivery system have a great influence on therapeutic efficacy. Some lipid and polymer constituents can trigger innate immune responses, which can increase adjuvant responses but can also decrease translation associated with excess stimulation. *ex-vivo* DC loading allows controlled immune activation but involves complex processing steps.

Fourth, the antigen presentation is affected by specificity and biodistribution. Passive targeting to the lymphoid tissues can be performed through nanoparticle-based systems, but direct antigen presentation can be obtained in the case of DC-based vaccines, which are less scalable.

Lastly, it is important that clinical translation is made possible by manufacturability, scalability and regulatory feasibility. LNPs platforms currently possess the most advanced large-scale production infrastructure, contributing to their dominance in ongoing clinical trials. Taken together, optimal vaccine efficacy depends on balancing stability, delivery efficiency, immune modulation, targeting precision, and translational scalability rather than relying on a single platform attribute. A structured comparison of major delivery systems is presented in Table 3.

Summing up, the selection of the delivery platform is as significant as the antigen design in defining the overall performance of the mRNA cancer vaccines. As summarized above in Table 2 and comparatively outlined in Table 3, LNP-based systems currently dominate clinical practice due to their superior stability, delivery efficiency, and scalable manufacturing. Nevertheless, polymeric carrier and DC-based method have its peculiar benefit in immune regulation and personalization. Further optimization and hybridization of delivery technologies will presumably increase potency, specificity and accessibility of cancer immunotherapy strategies in the future [49].

6. Clinical applications and case studies

The mRNA-based cancer vaccines have been demonstrated to have a wide range of clinical translation due to its flexibility, safety and immunogenicity, with an expanding clinical pipeline. Early-stage clinical trials have produced encouraging results in several malignancies and some of these are highly immunogenic (like melanoma) and others that are hardy to treat (like pancreatic cancer and glioblastoma). The studies put a strong focus on the potential of personalized mRNA vaccines, or on how these vaccines can generate lasting immune responses in case of strategic interaction with the other immunotherapy [50]. The application of personalized neoantigen vaccines against melanoma has been one of the most studied applications. These experiments involve sequencing of the tumors to detect mutations specific to the patient and transcription of mRNA constructs that encode different neoantigens [51]. These vaccines induced strong CD8 + and CD4 + T-cell responses in patients, and some patients had an extended progression-free period. One such example is the personalized neoantigen vaccine (BNT122/RO7198457) of BioNTech, which proved highly immunogenic and well-tolerated in early-phase clinical trials, and through which the use of additional combination with ICIs could be established [52,53].

Other cancer subtypes of breast cancer, including triple-negative breast cancer (TNBC) and others have also become targets of mRNA vaccine development. High mutational burden tumors or those that exhibit unique neoantigen profiles are good targets of personalized immunization [54]. Whether mRNA vaccines can activate tumor-specific T cells (in combination with PD-1/PD-L1 inhibitors) to overcome the immunosuppressive TME that defines advanced breast cancers is being tested clinically. mRNA vaccines have been tested to enhance antigen-specific T-cell infiltration in glioblastoma, a highly immunologically cold tumor [55]. Preclinical trial studies with LNP-formulated mRNA encoding TAAs showed that it could trigger immune responses in peripheral blood and tumor-infiltrating lymphocytes (TILs). Although

Table 3
Comparative evaluation of major mRNA cancer vaccine delivery platforms.

Delivery Platform	mRNA Protection	Endosomal Escape	Immunogenicity Profile	Targeting Precision	Scalability	Clinical Translation Status
LNPs	High	High (ionizable lipids)	Moderate controllable	Moderate (passive targeting)	Excellent	Clinically advanced
Polymeric Carriers (PEI, PLGA, dendrimers)	Moderate–High	Variable	Variable	Moderate	Moderate	Mostly preclinical
Electroporation	High (direct loading)	Direct cytosolic entry	Controlled	High (cell-specific)	Low	Limited clinical
Ex vivo DC Loading	High	Direct antigen presentation	Highly controlled	Very high	Low	Personalized trials
Hybrid / Targeted Nanoparticles	High (design-dependent)	Improved (engineered)	Adjustable	High (ligand-based)	Emerging	Early-stage

the clinical efficacy is still low, these experiments stretch proof-of-concept of mRNA vaccination even in severely immunosuppressive settings [56].

The other areas of interest are lung cancer and pancreatic cancer. mRNA vaccines based on neoantigens used alone or with ICIs or chemotherapy are in clinical trials in both metastatic disease and early-stage disease [57,58]. Preclinical models show that mRNA vaccination will be able to increase the populations of cytotoxic T-cells and synergize with immune-checkpoint blockade that may benefit the clinical outcomes. Along with personalized vaccines, mRNA vaccines based on common tumor antigens are being explored as off-the-shelf vaccines to benefit a larger patient population. Such vaccines encode antigens that are shared, such as Survivin, WT1, or MUC1 overexpressed in most cancers. Although they do not provide the personalization of neoantigen vaccines, these preparations are simpler to produce and enable the patient to begin treatment immediately, which is vital in the case of cancer patients with rapidly growing tumors [59].

Combination therapy has become one of the most important clinical applications. It entails the use of mRNA vaccines coupled with checkpoint inhibitors such as anti-PD-1 or anti-CTLA-4 antibodies to enhance T-cells activation and overcome tumor immunosuppression. Prior and early clinical evidence has revealed that this combination therapy can be used to complement the antitumor immune response in a manner neither of the two therapies can do individually [60]. The other pair under study are adjuvants, oncolytic viruses, and adoptive cell therapies, which can be perceived as a stable step toward achieving the inactivation of the immunity to its fullest capabilities, where treatment is tailored to the peculiarities of a particular tumor.

6.1. *Paradigm case studies informing clinical translation*

Some of the most popular clinical programs offer valuable insight into the aspects that may hasten the translation of mRNA cancer vaccines. Among them is mRNA-4157 (V940), which was developed by Moderna and Merck. It is a personalized neoantigen vaccine encoded by tumor sequencing data to include a maximum of 34 patient-specific neoantigens within one mRNA transcript. Coupled with pembrolizumab, early-phase experimental trials in melanoma showed improvement in recurrence-free survival among patients treated with the combination compared to checkpoint inhibition alone, which might reflect the significance of rational combination construction and biomarker-based patient selection [61].

Equally, the neoantigen vaccine BNT122 (RO7198457), developed through collaboration between BioNTech and Genentech, constructs individualized mRNA vaccines using next-generation sequencing together with computational epitope prioritization to suit specific patients. Clinical studies have demonstrated a robust CD4+ and CD8+ T-cell response, supporting the feasibility of scalable personalization [62]. In addition to the classical mRNA-LNP systems, other platforms that have been developed include Enteromix, which offers alternative approach to multi-antigen immunotherapy, focusing on extensive antigen coverage and immune response. These delivery methods are also grounded on engineered microbial vectors, but this does not invalidate the role of multi-epitope delivery in targeting, delivery efficacy, and combining with immune checkpoint blockade to generate meaningful clinical outcomes.

Collectively, these clinical case studies demonstrate the applicability of mRNA vaccines in cancer [63]. They are capable of being patient-specific to neoantigens and can be modified to target shared tumor antigens to be more broadly applicable and can be used in combination with complementary immunotherapies to address tumor immune evasion. Despite the fact that long term clinical efficacy and increased phase III trial evidence is yet to be announced, early evidence confirms the potential of mRNA vaccines being a disruptive modality in cancer therapy [64]. Table 4 presents an overview of clinical applications, combination strategies under investigation, and future directions for mRNA-based cancer vaccines.

7. Challenges and limitation

Despite immense potential of mRNA-based cancer vaccines, several scientific, technical, and clinical challenges are to be addressed to retrieve the full potential. These disadvantages should be taken into consideration not only by the researchers, but also by clinicians, as the discipline is about to be extended into clinical practice. One of the primary challenges is tumor heterogeneity and immune escape [65]. Cancers are phenotypically and genetically heterogeneous in different patients, as well as distinct tumors. This heterogeneity implies that a target-specific and attacking any specific antigens vaccine may fail to attack all the malignant cells since some subpopulation may develop resistance to immune surveillance. The tumors also have the ability to silence or delete the expression of the targeted antigens; a phenomenon has also been termed as antigen escape and reduce the effectiveness of the vaccines. Rational multi-epitope vaccine construction, addition of shared as well as patient-specific neoantigens and combination with real-time tumor genomic profiling are the developing solutions to this shortcoming. Alterative vaccine models that possess the ability to adjust the immunogen components according to tumor dynamics can also help to curb the evasion defenses and improve long-term immunotherapy [66].

Another limitation which is serious is efficiency in delivery. Although LNPs and other vectors have enhanced cellular delivery and integrity of mRNA, not all vaccine particles get to the target of APCs. Inefficient expression of the antigens can minimize the activation of T-cells and downplay the expression. Additionally, certain delivery platforms can cause unintended innate immunity responses, which can strengthen and weaken the effectiveness of vaccines depending on the situation. Striking the optimal balance between immunological stimulation and tolerability is a challenging issue of vaccine design [67]. Development of next generation ionizable lipids with better endosomal

Table 4
Clinical applications, combination strategies, and future innovations.

Application / Setting	Examples & Ongoing Trials	Combination Therapies	Future Directions	References
Melanoma	BNT122/RO7198457 (Phase I/II clinical trial).	ICIs (anti-PD-1, anti-CTLA-4)	AI-driven neoantigen prediction	50–53
Breast Cancer (TNBC)	Personalized mRNA vaccines under clinical testing (Phase I/II clinical evaluation).	With PD-1/PD-L1 blockade	Overcoming immunosuppressive microenvironment	25,54
Glioblastoma	LNP-formulated TAA-based mRNA vaccines (early Phase I clinical trials)	Adjuvants, immune modulators	Cold tumor reprogramming	55,56,87
Pancreatic / Lung Cancer	Neoantigen encoded mRNA vaccines + chemo or ICIs (Phase I clinical trials and exploratory studies)	Adoptive cell therapies, oncolytic viruses	Multi-omics-based antigen selection	57,58
General (Off-the-shelf)	WT1, MUC1, Survivin mRNA-vaccines (Phase I/II clinical studies)	Vaccine + checkpoint blockade	Biodegradable implants, targeted nanoparticles	59,78
Combination Therapies	Vaccine + PD-1, CTLA-4, oncolytic viruses (multiple early-phase clinical trials).	Immune reprogramming	Epigenetic, metabolic modulators	60,63,77

escape behavior, ligand targeted nanoparticles to deliver ligand to APC selectively, and biodegradable hybrid systems to tune innate immune activation are some of the emerging strategies to address these challenges. Nucleoside engineering and engineering of the UTRs also lead to increased efficiency of translation and the reduction of excessive innate sensing.

Immunosuppression by tumors is also a very formidable challenge. It is common to find that solid tumors produce an immunosuppressive microenvironment that is abundant in regulatory T cells, myeloid-derived suppressor cells and inhibitory cytokines [68]. The mRNA vaccines that are effective in priming tumor specific T cells when exposed to them can suppress antitumor activity, by rendering them dysfunctional when they enter the tumor. The combination therapies comprising immune checkpoint blockers, cytokine regulators, oncolytic viruses, or metabolic reprogramming agents that are currently under investigation with the aim of overcoming tumor-induced immunosuppression. Individualized combination protocols based on immune profiling and biomarker-mediated stratification can provide a more sensible paradigm to restore effective antitumor immunity [69]. Practically, it is difficult to manufacture and personalized neoantigen vaccines as they are based on tumor sequencing, computational predicted epitopes of immunogenic epitopes, and high-throughput production of a multiplex of mRNA constructs per patient. Even, if possible, this process is labor-intensive, costly and can slow down initiation of treatment. To address these logistical limitations, new developments in high throughput tumor sequencing, AI-guided neoantigen prediction, automated platforms of mRNA synthesis, and modular manufacturing pipelines are under development to reduce production times. Also, semi-personalized and shared neoantigen based vaccines are hybrid approaches that sustain balance between scalability and immunological specificity [70].

Lastly, stability and storage are also a technical barrier, with mRNA being inherently unstable and degradable and requiring cold-chain storage and a special formulation to preserve the integrity of the vaccine. Although the mRNA stability is remarkably increased using LNPs, long-term and long-distance storage and delivery, when resources are scarce, is also a problem that impedes the ubiquitous adoption of mRNA in clinical settings. Ongoing research into thermostable formulations, lyophilized mRNA vaccines, and improved lipid compositions may reduce cold-chain dependency and enhance global accessibility, particularly in low-resource settings.

7.1. Future paradigms for overcoming current barriers

The future development of mRNA cancer vaccines will probably be based on a combined paradigm that integrates precision oncology with the development of novel biomaterials, systems immunology, and AI. The multidimensional convergence of customized neoantigen design, novel smart delivery, biomarker-directed patient selection, and rational combination immunotherapy represents a strategy that can help overcome existing limitations. Rather than observing these challenges as a single impediment, a systems-based optimization strategy may enable mRNA cancer vaccines to move beyond experimental platforms and become part of standard cancer immunotherapy.

Conclusively, even though mRNA cancer vaccines are a paradigm shift in cancer immunotherapy, collective solutions to biological, technical as well as logistical obstacles are necessary to achieve successful clinical translation. Some of the priority areas include addressing the heterogeneity of tumors, improving the delivery precision, mitigating immunosuppressive microenvironment, simplifying the manufacturing process, and advancing formulation stability [71]. However, it is encouraging to note that these limitations are increasingly being turned by rapid developments on vaccine engineering, nanotechnology, computational biology, and combinational immunotherapy, into opportunities to innovate. As further interdisciplinary studies continue to refine mRNA cancer vaccines, they are destined to take over the central stage in the next-generation oncology therapeutics [72].

8. Future perspectives

The future of mRNA-based cancer vaccines is facing a spectacular one, which is made easy by the progress in genomics, bioinformatics, immunology, and drug delivery. The new generation of vaccines will be even more specific, effective and broad that can be used, particularly after the new technologies and models of personalized medicine are integrated, although preliminary clinical trials of them are rather safe and immunogenic [73].

8.1. AI in mRNA vaccine development

Machine learning and AI have a significant impact on various phases of developing the mRNA vaccine instead of being just an instrument of prediction of neoantigens. During the antigen discovery phase, AI-based algorithms have the ability to combine tumor sequencing information to rank neoantigens by MHC binding affinity, clonality, mutation burden and predicted T-cell receptor recognition. In addition to the epitope prediction, AI can support the optimization of the mRNA constructs design by simulating the UTRs, codon usage, and secondary structures and motivating the translational efficacy and success. During the clinical development phase, AI-based solutions can be involved in the examination of immune phenotyping, TME reads, and longitudinal reactional data to sort patients and identify responders and non-responders. This predictive modelling has the potential to facilitate adaptive personalization of vaccines and reasonable selection of combination therapy. In this way, AI can be used as a unifying system in developing antigens, optimization of constructs, patient selection, and predicting patient outcomes [74].

8.2. Multi-omics-guided antigen selection

Another paradigm related to the development of mRNA cancer vaccines is multi-omics integration. The integration of genomics (mutation profiling), transcriptomics (gene expression levels), proteomics (protein abundance), and immune-peptidomics (MHC-bound peptide presentation) can be used to better discover neoantigens that are mutated and expressed in high amounts and properly presented on tumor cells. Significantly, the combination of single-cell sequencing and spatial transcriptomics enables the mapping of the tumor heterogeneity and the presence of the immune cells forming the TME. The knowledge gained at the systems level can be used in the selection of multi-epitope vaccines that will target dominant and sub-clonal tumor populations at the same time. In addition, multi-omics data can also indicate how immunity evasion or tolerance can be facilitated, *e.g.* by the loss of antigen presentation packages or by increased expression of inhibitory pathways, thus informing rational combination therapy with immunomodulatory agents or ICIs [75].

8.3. Integrative development framework

In a practical developmental process, tumor biopsy would be sequenced quickly, followed by the AI-focused neoantigen prioritization process, multi-omics validation of antigen expression and presentation, and computational modelling of immune responsiveness. Those antigens would then be chosen as the neoantigens and inserted into stable and translation-optimized modular mRNA constructs. Simultaneous immune profiling would also help in the selection of combinational regimens depending on the TME in the patient. A pipeline of this nature can radically reduce the timescale of designing the vaccines as well as enhancing their accuracy and therapeutic efficacy [76].

8.4. Combination and delivery innovations

Combination strategies are expected to play a central role in the next generation of mRNA cancer vaccines. There is early evidence that when vaccines are used together with checkpoint-inhibitor, oncolytic viruses or adoptive cell therapies, tumor-mediated immunosuppression can be impressed, and T-cell activity can optimize (Fig. 3). Newer combinations are also in progress including vaccines combined with TGF-b inhibitors, metabolic modulators or epigenetic medications to reprogram the TME, to allow better immune targeting. Individual oncology is the final objective [77].

Technology breakthroughs in high-speed tumor sequencing, mRNA synthesis and delivery may enable development of actual patient specific vaccines in a week or within days of tumor biopsy. This approach can facilitate real-time response to tumor evolution, which overcomes the antigen escape and heterogeneity. In addition, the mRNA platforms that are rendered in modular format enable the addition of diverse care of antigens which enables multi-target vaccine, that is scalable and versatile [78]. Next generation delivery systems are also coming up. Besides lipid nanoparticles, researchers are also exploring targeted nanoparticles targeting DCs with mRNA, targeted release biodegradable polymers, and even implantable devices, which can maintain antigen expression in the long run. The innovations are intended to improve the immunogenicity, reduce the dose, and improve the clinical usability of mRNA vaccines. Finally, technology will most probably transform regulatory and manufacturing systems [79]. The COVID-19 pandemics demonstrated that it can be manufactured on a broader scale, faster and quality-controlled in large quantities of mRNA across the globe. Using these lessons in the sphere of oncology, one will be able to translate clinical studies faster in relation to the treatment personalized as it requires agile pipelines of production [80].

Generally, the convergence of computational intelligence and systems biology together with the development of innovative biomaterials and precision oncology bring hope to the future of mRNA-based cancer vaccines. AI-based design, multi-omics-based antigen selection, adaptive combination immunotherapy and next-generation delivery systems can convert proof-of-concept to ones that are clinically validated. Even with the obstacles, the concerted development of biological understanding and technological creativity brings mRNA vaccines as a blockbuster of the next-generation personalized cancer immunotherapy [81].

9. Emerging advances in next-generation mRNA cancer vaccines

The last few years perceived significant improvements in next-generation mRNA cancer vaccine technologies, which occurred as a result of molecular engineering, immunology, delivery system and computational biology improvements. New clinical and translational evidence is pointing to a marked departure of initial proof of concept platforms into precision-engineered vaccines with better immunogenicity, durability and therapeutic potential (Fig. 4). Individualized neoantigen-based immunization drugs have also shown promising results in melanoma and other solid tumors. When combined with ICIs, they have demonstrated signs of increased tumor-specific T-cell activity and improved relapse-free survival in initial phase trials. These findings support the clinical viability of personalized vaccine systems such as BNT116 and others. Parallel advancements in the field of RNA engineering have led to the development of saRNA constructs, which can replicate RNA intracellularly, thus, reducing the amount of dose, which is needed to activate, while extending antigen expression. Moreover, circular RNA data provides stability and exonuclease resistance levels and therefore, extend translational activity and potentially reduce the required frequency of re-dosing. These new mRNA designs are significantly advanced to an absence of traditional constraints of linear mRNA molecules [82].

Vaccine design can also bring transformation as a result of

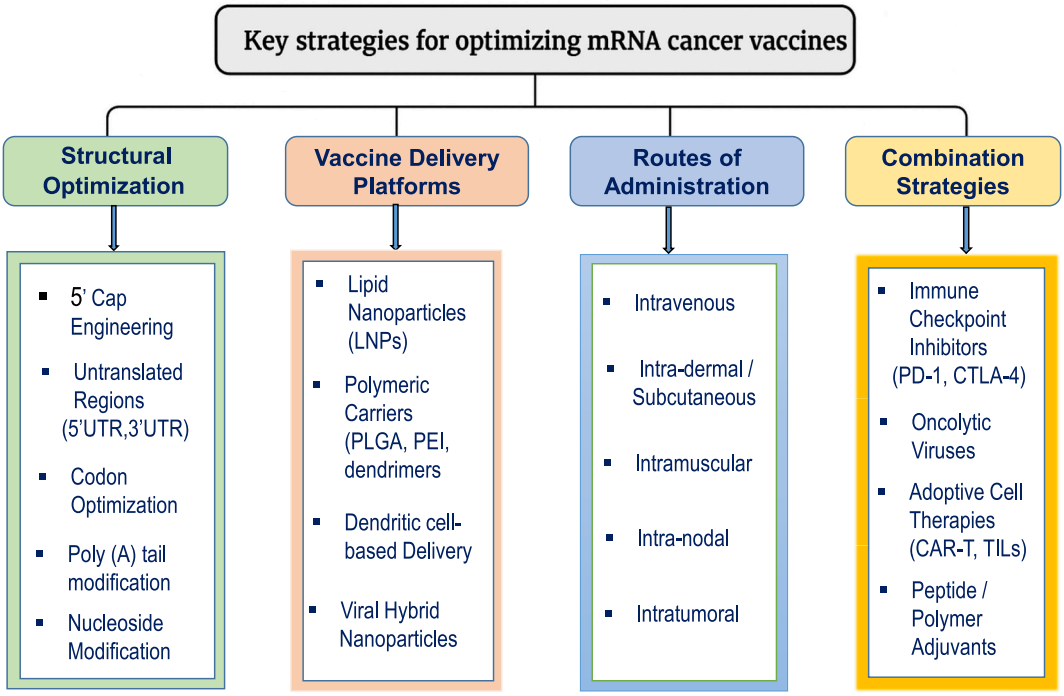

Fig. 3. Combination strategies and structural optimization of mRNA cancer vaccines.
mRNA vaccines are increasingly being used in combination with other therapeutic strategies such as ICIs, cytokines, radiotherapy, and chemotherapy. These approaches help target tumors more effectively and overcome tumor-induced immunosuppression, thereby enhancing antitumor activity through synergistic mechanisms. At the same time, structural optimization of mRNA—including improvements in the 5′ cap, UTRs, codon usage, nucleoside modifications, and poly(A) tail length—has significantly increased mRNA stability, translational efficiency, and immunogenicity. Together, these advances highlight the dual strategy of maximizing the therapeutic potential of mRNA-based cancer immunotherapy through rational vaccine design and combination treatment regimens.

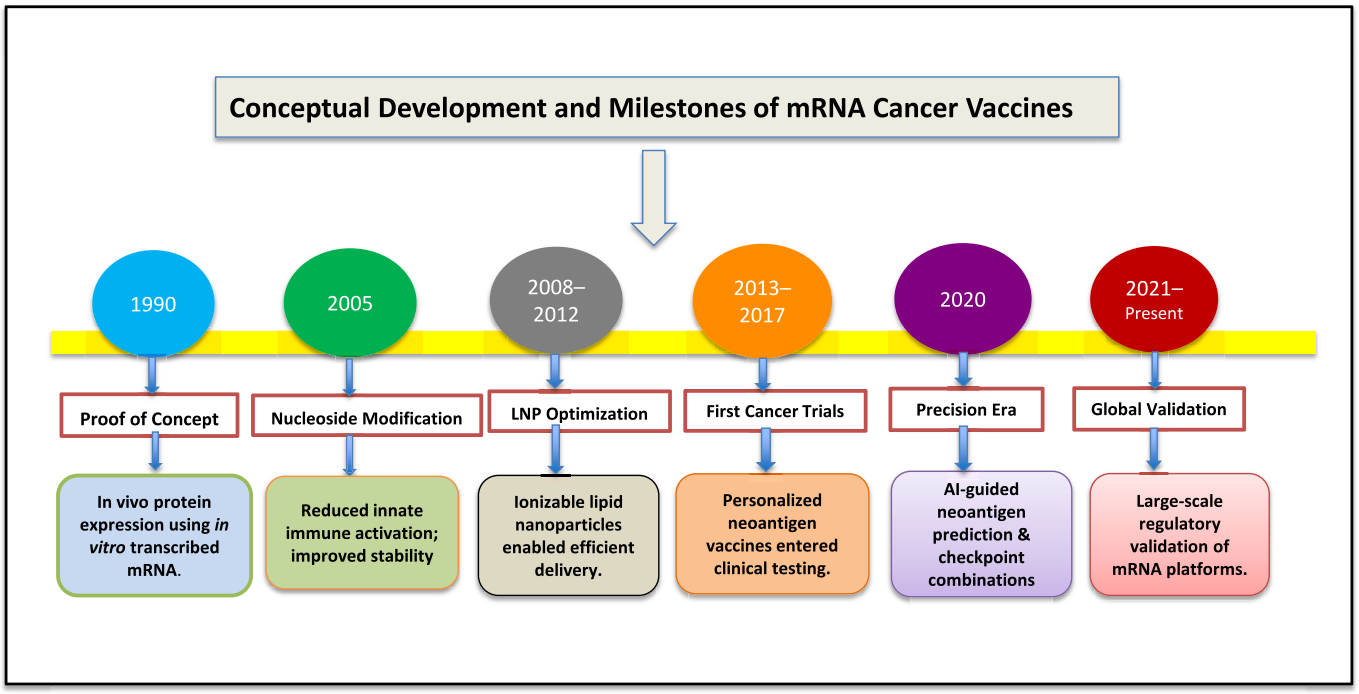

Fig. 4. Conceptual progression and translational development of mRNA cancer vaccines.
The development of mRNA-based cancer vaccines has progressed from early proof-of-concept studies demonstrating *in vivo* protein expression to the current precision oncology platforms. Innovations such as nucleoside modifications have improved stability and reduced excessive innate immune activation, while advances in ionizable LNPs delivery systems have enabled efficient cytosolic delivery and facilitated clinical translation. These breakthroughs expanded early neoantigen vaccine studies and accelerated regulatory validation of mRNA platforms. More recent developments integrate personalized tumor profiling, combination immunotherapies, and AI-assisted neoantigen prediction, reflecting the transition toward precision-guided and personalized mRNA cancer vaccination strategies.

computational and data-driven approaches. Neoantigen prediction algorithms based on AI have now incorporated multi-omics information, such as tumor sequencing, predicted MHC binding affinity, and immunogenicity modelling to perform candidate selection and personalize vaccine construct in a significantly more targeted manner. There is a growing trend toward real-time adaptive design methods, where optimization of the selection of epitopes is done on a recurring basis based on the tumor evolution and status of the host immune system [83]. The delivery systems have also made notable improvements. Advanced biodegradable ionizable lipids, polymer lipid hybrids and targeted nanoparticles are now under development to improve tissue targeting, enhance cytosolic release as well as reduce systemic reactogenicity. The combination of these delivery inventions, together with modular vaccine design systems, is intended to enhance safety as well as therapeutic efficacy in both types of cancer [84].

Together, these technological and biological developments signify the shift in the first-generation mRNA vaccine platforms to extremely optimized and precision-engineered immunotherapeutic modalities. The combination of enhanced RNA constructs, higher delivery systems, AI-inspired design, and rational combination approaches is still expanding the current mRNA cancer therapeutic area, bringing them nearer to virtual clinical applicability in a wide range of malignancies [85].

10. Conclusion

Cancer vaccination based on mRNA is a paradigm shift in cancer therapy as it provides the specificity of personalized medicine and the flexibility and power of modern immunotherapy. These immunizations convey either tumor or patient-specific neoantigens that offer the genetic information of said antigens resulting in the body producing its own antigens and thus effective and combinatory adaptive and innate immune responses. The mRNA formulations unlike the conventional cancer vaccines are non-integrative, safe, highly modular, and may be developed quite rapidly, particularly in respect to the personalized and multi-epitope methods [86].

Clinical trials have tested and demonstrated the mRNA vaccines against malignancies comprising of melanoma and breast cancer along with glioblastoma and pancreatic cancer [87]. Preliminary results have demonstrated that they can produce strong cytotoxic T-cell responses and when combined with ICIs or other immunotherapies, they would have made good synergies that may in theory break tumor-mediated immunosuppression. Nevertheless, concerns like heterogeneity of tumors, antigens evasion, delivery efficacy and logistics exist that require to generate one tumor product [88].

The upcoming developments that can be used to enhance the effectiveness, personalization and scalability of vaccines are AI, multi-omics, integrated delivery, and combination treatment. These advances are indicative of the future of mRNA cancer vaccines becoming a fundamental part of precision oncology and offer tailored, versatile, and efficient immunotherapies that can keep up with the adaptive and dynamic aspect of tumors [89]. Currently, research and technology continue to advance, and mRNA-based vaccinations have the capability to transform the manner in which cancer treatment is conducted, bringing one step closer to not only effective but also highly personalized and safe cancer treatment [90].

Clinical significance

This review highlights the clinical significance of mRNA-based cancer vaccines as a transformative approach in oncology, emphasizing their ability to generate personalized, tumor-specific immune responses with high safety and scalability. It underscores the potential of these vaccines to enhance patient outcomes, particularly when combined with ICIs or other immunotherapies, and their role in overcoming tumor heterogeneity and immune evasion in various cancers.

CRediT authorship contribution statement

PG; SSS: had the idea for the article and performed the literature search, and writing - original draft preparation.

RS; SSS: final review and editing.

All authors read and approved the final manuscript.

Consent for publication

Not applicable.

Ethics approval

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Declaration of competing interest

The authors declare no conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbcan.2026.189577.

Data availability

No data was used for the research described in the article.

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