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REVIEW

mRNA vaccines in cancer immunotherapy: current progress and perspectives in solid tumors and hematologic malignancies

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Abstract **The unprecedented success of mRNA vaccines during the COVID-19 pandemic has accelerated the development of nucleic acid–based therapeutics, particularly in oncology. Decades of foundational research on mRNA design, delivery, and immunogenicity have laid the groundwork for the application of mRNA vaccines in cancer treatment. Herein, we summarize the key principles of synthetic mRNA engineering, including the optimization of structural elements, nucleoside modification, and codon usage to improve stability, enhance translation efficiency, and modulate immune responses. We highlight diverse antigen strategies, including tumor-associated antigens; neoantigens; and novel sources, such as cryptic antigens, aberrant splicing variants, and transposable element-derived antigens. We discuss delivery platforms, particularly lipid nanoparticles (LNPs) and dendritic cell-based systems, in the context of improving mRNA biodistribution and immune activation. We further examine how mRNA vaccines stimulate antitumor responses by encoding antigens, modulating the tumor microenvironment, and supporting adoptive T cell therapies. We review preclinical and clinical advances in combining mRNA vaccine with immune checkpoint inhibitors for the treatment of solid tumors (e.g., melanoma, pancreatic cancer, and glioblastoma) and hematologic malignancies (e.g., acute myeloid leukemia, myelodysplastic syndrome, and multiple myeloma). Finally, we explore emerging innovations, such as targeted LNP platforms for *in vivo* chimeric antigen receptor T/T cell receptor T engineering and artificial intelligence–assisted vaccine design, underscoring the transformative potential of mRNA technology in cancer immunotherapy.**

Keywords mRNA vaccine; cancer immunotherapy; solid tumors; hematological malignancies; neoantigens; lipid nanoparticles; clinical trials

Introduction

Cancer is the second leading cause of mortality worldwide and continues to pose a major challenge to global health [1,2]. Although current cancer treatments, including surgery, chemotherapy, radiotherapy, and targeted therapies, have seen remarkable progress, they are often hindered by limitations, such as invasiveness, drug resistance, and treatment-related side effects, resulting in their unsatisfactory overall efficacy and long-term outcomes for many cancers [3–6]. In recent years, cancer immunotherapy has emerged as a transformative approach in oncology, with immune checkpoint inhibitors (ICIs) achieving remarkable success in several cancer types [7,8]. However, the clinical benefit of ICIs is limited to a subset of patients, and their efficacy is often hindered by resistance mechanisms [9–11]. These limitations highlight the urgent need for novel, effective, and personalized immunotherapeutic strategies.

mRNA has rapidly gained attention as a promising therapeutic platform, particularly following its unprecedented success during the COVID-19 pandemic [12,13]. The widespread application of mRNA vaccines against SARS-CoV-2 provided the large-scale, real-world validation of the technology’s safety, efficacy, and scalability, highlighting their potential in oncology [14–16]. mRNA vaccines offer several advantages over traditional vaccine modalities. These advantages include high safety, rapid and cost-effective development, strong immunogenic potential, and the ability to induce cellular

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and humoral immune responses: features that are especially critical for effective antitumor immunity [17–21]. In cancer immunotherapy, mRNA vaccines can be engineered to encode tumor-specific antigens (TSAs) or tumor-associated antigens (TAAs), thereby priming the immune system to recognize and eliminate malignant cells [22–24]. mRNA therapeutics extend beyond vaccines to include mRNAs that encode cytokines [25–28], immune modulators [29–31], and even components for genome editing [32,33] or adoptive cell therapies, such as chimeric antigen receptor T (CAR-T) or T cell receptor T (TCR-T) cells [34–36].

While the majority of mRNA cancer vaccine research has focused on solid tumors, including melanoma, pancreatic ductal adenocarcinoma (PDAC), non-small cell lung cancer (NSCLC), prostate cancer, and glioblastoma (GBM), interest in their application in hematologic malignancies is growing [37–40]. Systemic delivery routes, such as intravenous or intramuscular injection, naturally expose mRNA therapeutics to antigen-presenting cells (APCs), particularly DCs and macrophages, which efficiently internalize and translate mRNA. The translated antigens are presented on MHC class I and II molecules, thereby activating cellular and humoral immune responses. This approach harnesses the body's immune system for precise tumor targeting while minimizing off-target toxicity [18,19]. Recent advances in mRNA stabilization, immunogenicity optimization, and especially lipid nanoparticle (LNP)–based delivery systems have markedly improved mRNA stability, cellular uptake, and antigen expression [14,41]. These innovations collectively support the feasibility of mRNA-based cancer immunotherapies and highlight the importance of evaluating their current progress, existing limitations, and future potential across diverse tumor types.

The journey of mRNA technology from a foundational scientific concept to a transformative clinical reality has been marked by several decades of pivotal breakthroughs. As illustrated in Fig. 1, landmark advances, such as the discovery of nucleoside modifications to reduce immunogenicity, the engineering of advanced LNP delivery platforms, and the large-scale clinical validation of the platform during the COVID-19 pandemic, have collectively paved the way for its current application in cancer immunotherapy. These milestones reflect the synergistic integration of molecular biology, materials science, and immunology, laying a robust groundwork for the next generation of personalized mRNA cancer vaccines.

In this review, we aim to provide a comprehensive overview of the current trend of research on mRNA vaccines and relevant therapeutics in cancer, including solid tumors and hematological malignancies. While highlighting the latest clinical advances, technical innovations, and delivery systems, we also discuss the critical role of blood and immune system interactions in shaping the efficacy, distribution, and safety of mRNA-based interventions. The rapidly evolving field of mRNA cancer immunotherapy holds promise to shift the therapeutic paradigm and offers new hope for personalized cancer treatment.

mRNA vaccine design and optimization

Key structural components of mRNA and their functional roles

Synthetic mRNA, also known as *in vitro*–transcribed (IVT) mRNA, is meticulously designed to mimic the structure of natural eukaryotic mRNA, ensuring its stability, efficient translation, and reduced immunogenicity [13,58,59]. A typical IVT mRNA molecule comprises several key structural components, each with a distinct and crucial functional role: a 5′ cap, 5′ and 3′ untranslated regions (UTRs), an open reading frame (ORF), and a poly(A) tail [60].

5′ Cap

The 5′ cap is a modified guanine nucleotide added to the 5′ end of the mRNA. Its primary functions include enhancing mRNA stability and facilitating efficient translation initiation [61,62]. The 5′ cap and 3′ poly(A) tail work synergistically to ensure optimal mRNA translation *in vivo* [63]. Specifically, a Cap 1 structure, which is methylated at the ribose 2′-O position of the first nucleotide, has been shown to possess superior *in vivo* properties compared with a Cap 0 structure [64,65]. Inefficiencies in capping can lead to the rapid degradation of uncapped mRNA and potentially trigger undesirable immune responses, thereby reducing therapeutic efficacy [23,66].

UTRs

UTRs are noncoding sequences located at the 5′ and 3′ ends of the mRNA, flanking the ORF. The 5′ and 3′ UTRs play critical roles in modulating mRNA stability and translation efficiency [67]. Their optimization can markedly enhance the expression level of the target protein [67–69].

ORF

The ORF is the central coding region of the mRNA molecule, containing the genetic code that specifies the amino acid sequence of the desired protein. During translation, ribosomes use the ORF as a template to assemble amino acids into the target peptide or protein.

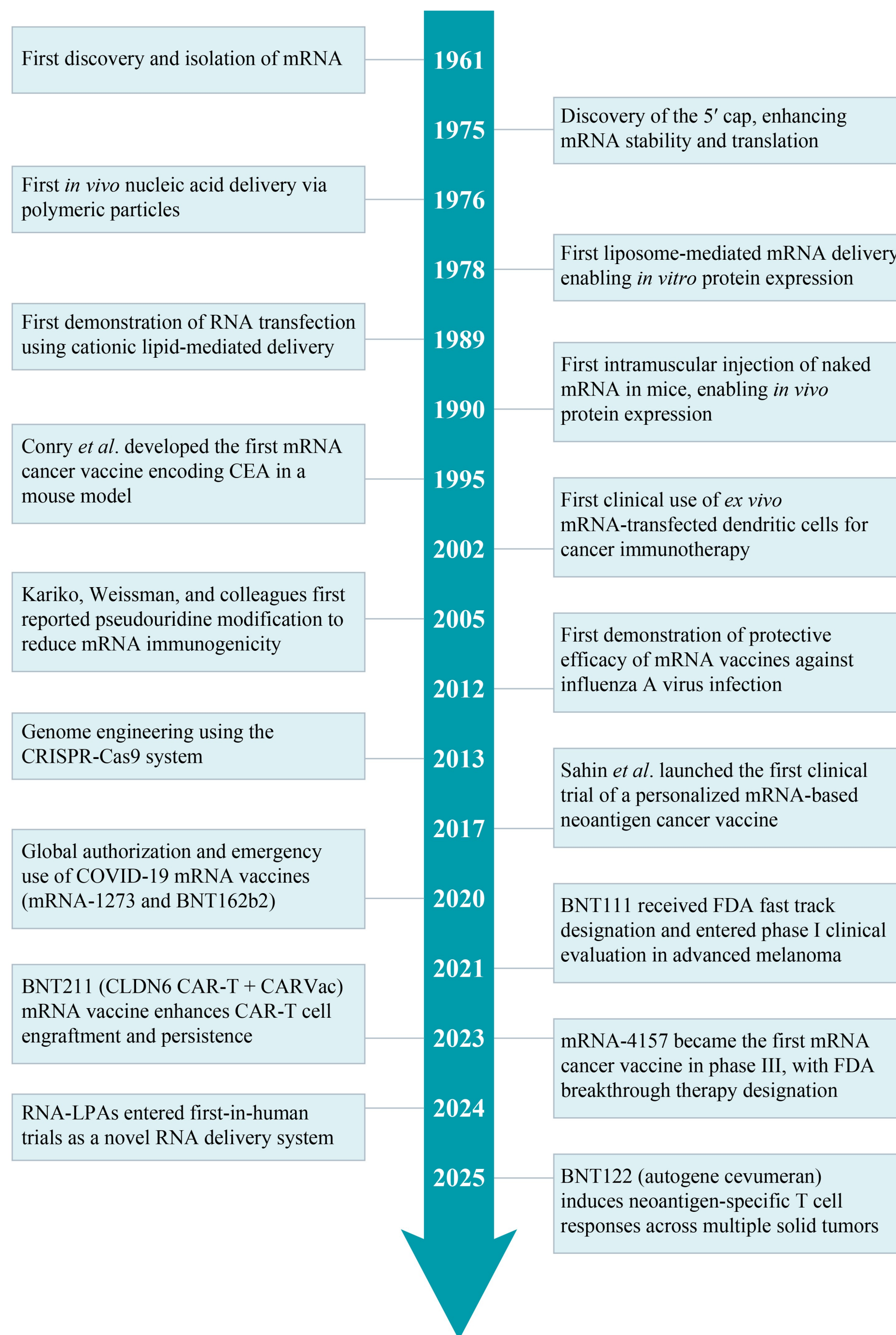

Fig. 1 Timeline of key milestones in the development of mRNA cancer vaccines. The journey of mRNA vaccines from a foundational biological discovery to a transformative clinical platform has been marked by several decades of pivotal innovation. The initial era, spanning from the discovery of mRNA in 1961 [42] and its 5′ cap in 1975 [43] to the first successful *in vivo* protein expression via direct mRNA injection in 1990 [44], established the core scientific principles of the field. The field's therapeutic potential began to materialize in the context of cancer immunotherapy with the first preclinical cancer vaccine model in 1995 [45] and the clinical use of mRNA-transfected dendritic cells in 2002 [46]. A critical turning point came in 2005 with the discovery by Kariko, Weissman, and colleagues that pseudouridine modification could dramatically reduce mRNA immunogenicity [47], solving a key hurdle for the therapeutic use of mRNA. This breakthrough, combined with advances in delivery systems, such as cationic lipids [48], and the launch of genome engineering tools, such as CRISPR-Cas9 [49], paved the way for the first personalized neoantigen cancer vaccine trial in 2017 [50]. The unprecedented success and global authorization of COVID-19 mRNA vaccines in 2020 [51–53] served as a massive validation of the platform's safety and scalability, catalyzing a new wave of innovation. This situation has led to rapid progress in the cancer field, highlighted by BNT111 receiving FDA fast track designation in 2021 [54]; mRNA-4157 becoming the first mRNA cancer vaccine to enter a phase III trial in 2023 [55]; and the emergence of next-generation approaches, such as RNA–LPAs [56] and CAR-T [57] combination therapies.

Poly(A) tail

The poly(A) tail is a stretch of approximately 150 adenine nucleotides added to the 3′ end of the mRNA [60]. It is crucial for mRNA stability and plays a vital role in the formation of a translation-competent ribonucleoprotein complex. An extended poly(A) tail, within an optimal length range (for instance, a length of 100–150 nucleotides has been reported as an optimal range), is generally associated with improved translational efficiency [14,70].

The individual structural components of mRNA are not isolated elements but form a highly integrated and dynamic system. Therefore, optimization efforts must consider the entire mRNA molecule as a dynamic entity rather than focusing on isolated parts. Furthermore, the inherent fragility and instability of mRNA necessitate the meticulous design and modification of these structural elements. Ongoing research into optimal lengths, sequences, purification to remove uncapped mRNA and double-stranded RNA (dsRNA), and specific modifications indicates that no universal "one-size-fits-all" solution exists [64–67,71,72]. Each therapeutic application may require the specific fine-tuning of these components for maximal performance, underscoring the continuous need for tailored design and optimization.

Types of mRNA vaccines: conventional, self-amplifying, *trans*-amplifying, and circular RNA

The field of mRNA therapeutics is continuously evolving, moving beyond conventional nonamplifying mRNA toward increasingly complex and promising formats, such as self-amplifying mRNA (saRNA), *trans*-amplifying mRNA (taRNA), and circular RNA (circRNA) (Fig. 2 and Table 1). These efforts aim to overcome the inherent limitations of mRNA, such as transient expression and high dosing requirements, by leveraging replication and circularization mechanisms, offering increased potency, durability, and cost-efficiency.

Conventional mRNA is the standard linear mRNA molecule currently utilized in approved vaccines, such as those for COVID-19 (BNT162b2 and mRNA-1273) [51–53]. Although translated by the host cell's ribosomes and effective for rapid immune responses, its expression

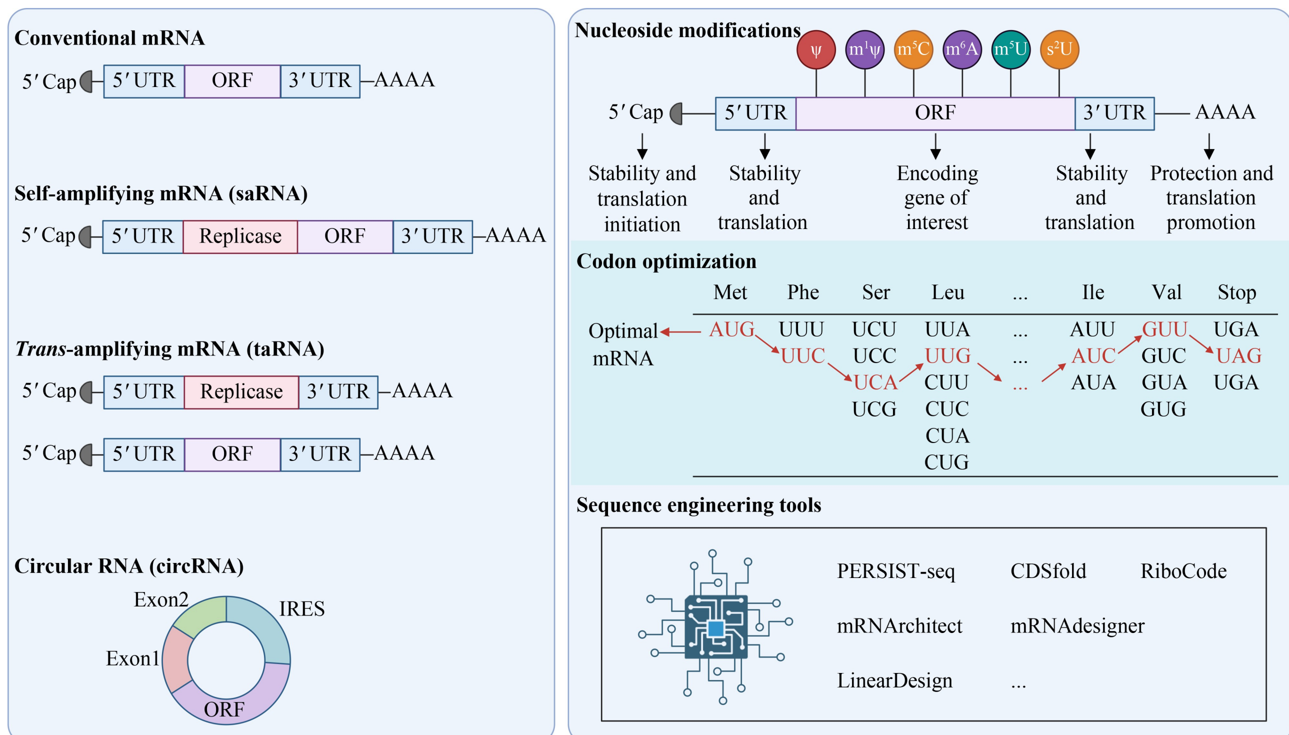

Fig. 2 Overview of mRNA vaccine platforms and optimization strategies. The left panel illustrates four main types of synthetic RNA used in mRNA vaccines: conventional mRNA, self-amplifying mRNA (saRNA), *trans*-amplifying mRNA (taRNA), and circular RNA (circRNA). All platforms share key structural elements, such as a 5′ cap, untranslated regions (UTRs), and open reading frames (ORFs). saRNA and taRNA include replicase sequences to enable intracellular RNA amplification, whereas circRNA forms a closed-loop structure and relies on an internal ribosome entry site (IRES) for cap-independent translation. The right panel highlights major optimization strategies, including nucleoside modifications, codon optimization, and structure-based design using tools, such as LinearDesign and mRNAarchitect. These approaches aim to improve mRNA stability, translation efficiency, and protein yield while minimizing innate immune activation, thereby enhancing the effectiveness of mRNA-based therapies. This figure was created with BioRender.

Table 1 Comparison of mRNA vaccine types

Type	Structure	Mechanism	Advantages	Challenges
Conventional mRNA	Linear, 5′ cap, untranslated regions (UTRs), open reading frame (ORF), poly(A) tail	Direct translation by host ribosomes	High safety; fast, scalable, and cost-effective production; low toxicity	Transient expression; requires high dosing; instability
Self-amplifying mRNA (saRNA)	Linear, 5′ cap, UTRs, ORF (encoding nsP1–4 replicase and antigen), poly(A) tail, subgenomic promoter	nsP1–4 is translated into RDRP, which replicates saRNA and subgenomic RNA, leading to amplified antigen expression	Dose-sparing effect; long-lasting effects; robust immunity	Long sequence (9–12 kb); production/delivery challenges because of size
Trans-amplifying mRNA (taRNA)	Two linear RNAs: one encoding the replicase genes (RDRP), and the other encoding the gene of interest (transgene)	RDRP amplifies the target gene of interest, leading to amplified antigen expression	Overcomes saRNA size challenges (production, delivery, and stability); enhanced immune responses with minimal RNA	Requires the codelivery of two distinct RNA molecules
Circular RNA (circRNA)	Covalently closed continuous loop, lacks 5′/3′ ends, contains internal ribosome entry sites (IRESs), ORF, spacers	Ribosome recruitment via IRESs (cap-independent), rolling circle translation is possible	Enhanced stability; long half-life; prolonged protein expression; reduced dosing frequency	Requires IRESs for translation; complex synthesis/purification

is typically transient [73]. Beyond the standard linear mRNA elements (a cap, UTRs, and a poly(A) tail), saRNA contains a 5′ end ORF encoding four nonstructural proteins (nsP1–4) that form an RNA-dependent RNA polymerase (RDRP). The enzyme self-amplifies the target mRNA transcript within the cell, resulting in substantially enhanced antigen translation. The key advantages of saRNA lie in its self-replicating nature, enabling high protein expression with low mRNA doses (known as the “dose-sparing effect”) and prolonged therapeutic effects [74,75]. taRNA consists of two separate RNA molecules: one encoding replicase genes (RDRP) and the other encoding the gene of interest (transgene). By separating the replicase and transgene, taRNA reduces the risk of viral protein generation and offers high translational and replication efficiency [76,77]. circRNA forms a covalently closed loop lacking 5′ and 3′ ends. This characteristic protects it from exonuclease degradation and confers high stability. Translation is initiated via an internal ribosome entry site (IRES), enabling cap-independent protein synthesis. The key advantages of circRNA include enhanced stability, prolonged half-life, and sustained protein expression, making it especially promising for applications requiring long-term expression, such as in cancer cells [78].

While conventional mRNA remains the most clinically validated platform for rapid vaccine deployment, self-amplifying formats (saRNA and taRNA) provide superior antigen expression and dose-sparing benefits because of their self-replicating mechanisms. However, these amplification systems may introduce additional complexity in manufacturing and raise potential innate immune activation concerns. By contrast, circRNA offers remarkable stability and sustained expression with a reduced inflammatory profile, although its translational efficiency and large-scale production still require optimization. Overall, each platform carries unique strengths and trade-offs: conventional mRNA suits acute infections demanding fast responses; saRNA/taRNA may be preferable for indications requiring sustained expression or reduced dosing; and circRNA shows promise for durable, long-term therapies, such as cancer immunization [16,20,34].

Optimization strategies: nucleoside modifications, codon optimization, and sequence engineering

mRNA optimization strategies, including nucleoside modifications, codon optimization, and sequence engineering (covering elements such as UTRs, cap, and poly(A) tail), are crucial for maximizing therapeutic potential by improving stability, translational efficiency, and modulating immunogenicity (Fig. 2). However, mRNA optimization is a complex process involving trade-offs: improving one property may compromise another. For instance, while codon optimization aims for increased expression, it can paradoxically affect protein function or immunogenicity [79]. These complexities underscore the need for a multidisciplinary design approach rather than optimizing individual parameters in isolation.

Nucleoside modifications

Nucleoside modifications are critical and indispensable for optimizing the function of mRNA in therapeutic applications. For example, pseudouridine (ψ) and N1-methylpseudouridine (m1ψ) are frequently mentioned and were notably used in COVID-19 vaccines (such as BNT162b2 and mRNA-1273) [12,15,72,80]. Other key modifications include 5-methylcytidine (m^5C), N6-methyladenosine (m^6A), 5-methyluridine (m^5U), and 2-thiouridine (s^2U) [19,81,82]. Collectively, these modifications enhance mRNA stability; increase

translation efficiency; and reduce immunogenicity by preventing recognition by innate immune sensors, such as Toll-like receptors (TLRs) and RIG-I [14,47,83].

Codon optimization

Codon optimization improves ribosome engagement and translation efficiency by replacing synonymous codons preferred by the host organism [41,84,85]. This approach enhances protein expression by minimizing undesirable mRNA secondary structures (e.g., lowering minimum free energy or hairpins) and facilitating efficient elongation. Additionally, uridine depletion, which is achieved by increasing GC content through codon optimization, has been employed by CureVac to reduce innate immune activation and enhance mRNA stability [14,68]. Machine learning (ML) models, such as RiboNN, trained on large-scale ribosome profiling and RNA-seq data, now enable the predictive assessment of translation efficiency directly from sequence context [86].

Sequence engineering tools

Beyond individual modifications and codon optimization, holistic sequence engineering approaches are crucial for comprehensive mRNA design. Tools, such as CDSfold [87] and PERSIST-seq [88], minimize mRNA free energy and simplify complex multiloop structures, thereby improving mRNA stability and half-life. Deep learning frameworks (e.g., RiboCode [84]) and design platforms (e.g., mRNArchitect [89], mRNAdesigner [90], and LinearDesign [91]) integrate parameters, such as GC content, secondary structure, and uridine depletion, to achieve multiobjective optimization. Collectively, these tools aim to enhance mRNA stability, translation efficiency, and maximize protein expression levels while reducing immunogenicity, laying the foundation for artificial intelligence (AI)–assisted, fully automated mRNA engineering pipelines.

AI-driven design of personalized mRNA vaccines

The design of personalized mRNA cancer vaccines has evolved into a data-driven, multistage process fundamentally powered by computational biology and AI. This *in silico* workflow, which is central to developing truly patient-specific therapies, can be broadly divided into two key phases: antigen discovery and mRNA engineering [92]. The first phase centers on AI-assisted neoantigen prediction. While the next-generation sequencing of each patient's tumor reveals thousands of somatic mutations, only a few yield immunogenic epitopes. AI and ML frameworks, trained on large immunopeptidomics data sets, are now indispensable for narrowing this search. Tools, such as NetMHCpan, and resources, such as the Immune Epitope Database, can be leveraged. These algorithms and resources integrate peptide–MHC binding, antigen processing, and presentation likelihood to prioritize neoantigen candidates most likely to elicit potent T cell responses [93]. This computational filtering defines the immunological "blueprint" for each personalized vaccine. Once optimal antigenic targets are selected, the focus shifts to mRNA sequence optimization. Beyond codon adaptation, advanced algorithms, such as RNAfold, mFold, and LinearDesign, computationally model mRNA secondary structures to enhance stability and translational efficiency. Complementary codon optimization tools (JCAT and GeneOptimizer) refine sequence composition to align with host tRNA abundance, thereby maximizing protein yield. Increasingly, deep learning–based approaches perform this multiparameter optimization holistically, treating the mRNA as a tunable molecular system engineered for high-fidelity antigen expression. Furthermore, emerging studies have extended AI's utility to nanoparticle formulation, where ML models (e.g., XGBoost and deep neural networks) predict how lipid composition, particle size, and charge influence mRNA encapsulation, biodistribution, and immunogenicity [92,94]. Collectively, this integrated, AI-driven design paradigm is transforming the development of personalized mRNA vaccines, making it faster, more predictive, and more rational compared with traditional approaches.

Delivery systems for mRNA therapeutics

The successful clinical translation of mRNA therapeutics relies on the development of effective delivery systems. Naked unmodified mRNA is inherently unstable and prone to rapid degradation by RNases in blood and tissues. Its large size, negative charge, and hydrophilic nature hinder its ability to cross the cell membrane [18,34,95]. Therefore, effective delivery systems are essential to protect mRNA, facilitate cell-specific targeting and uptake, and ensure its successful translation into proteins. These systems primarily fall into two categories: nanoparticle-based and cell-based delivery systems (Table 2).

Nanoparticle-based delivery systems

mRNA–lipid nanoparticles

mRNA–lipid nanoparticles (RNA–LNPs) are the most widely used and clinically advanced mRNA delivery vehicles. They encapsulate mRNA molecules within lipid vesicles to protect them from degradation and facilitate cellular uptake and intracellular release. Approved COVID-19 mRNA vaccines (e.g., Moderna's mRNA-

Table 2 Comparison of major mRNA vaccine delivery systems

Type	System	Core mechanism	Key advantages	Challenges	Representative examples
Nanoparticle based	mRNA–lipid nanoparticles (RNA–LNPs)	Encapsulate mRNA in lipid vesicles to prevent degradation, enter cells via endocytosis, escape from endosomes, and complete translation	Most advanced in clinical development, good protection, efficient cellular uptake, verified safety	No major challenges, current mainstream platform	Moderna mRNA-1273 and Pfizer/BioNTech BNT162b2
	Anionic mRNA lipoplexes (RNA–LPXs)	Target dendritic cells (DCs) in secondary lymphoid organs, are taken up via macropinocytosis, activate the IFN-α signaling pathway, and further promote antigen presentation and specific T cell expansion	Precise DC targeting, no need for additional ligand modification, potent activation of specific T cells	No major challenges identified yet	BioNTech BNT111 (FixVac), and BNT122 (iNeST)
	Multilamellar mRNA–lipid particle aggregates (RNA–LPAs)	Activate RIG-I receptors in stromal cells, promote cytokine release and immune cell migration, and ultimately trigger antitumor immune responses	Enhance antigen immunogenicity, remodel tumor microenvironment, and improve survival (early data)	In the early clinical trial stage, limited clinical data were accumulated	In clinical trials for glioblastoma
	Protamine–mRNA complexes	Bind mRNA via electrostatic interaction to prevent degradation and activate innate immunity, with sequence optimization further enhancing expression and immune effects	Laid the foundation for mRNA vaccine development, good tolerability, and immune activation ability	Issues with consistency and tolerability, limited therapeutic benefit; replaced by LNPs as mainstream delivery method	CureVac's RNActive® platform (e.g., CV9104 and CV9202)
	Virus-like particles (VLPs)	Mimic viral structure to encapsulate mRNA for DCs-targeted delivery, with no risks of viral replication or genomic integration, and some variants are applicable for gene editing	High safety, excellent lymphoid organ targeting, strong immunogenicity, and extensible to gene editing	No major challenges identified yet	DVLP and mLP-CRISPR (for gene editing)
Cell based	RNA-loaded DCs	Transfect mRNA into autologous DCs via electroporation *ex vivo*, where DCs translate and present antigens through MHC class I/II molecules to activate specific T cells	High personalization, suitable for low-immunogenic/antigen-sparse tumors, activates comprehensive cellular immunity	Complex manufacturing, low lymph node homing efficiency, variable clinical efficacy; shifting to *in vivo* platforms	Clinical trials in acute myeloid leukemia, melanoma, and glioblastoma

1273 and Pfizer/BioNTech's BNT162b2) have successfully utilized LNP technology [51–53]. Typical LNPs consist of four main components: ionizable lipids, helper phospholipids, cholesterol, and PEGylated lipids [14,41]. Ionizable lipids, such as SM-102 (used in Moderna's vaccine) and ALC-0315 (employed in Pfizer/BioNTech's vaccine), are crucial because they bind to negatively charged mRNA in acidic environments (e.g., endosomes) and become neutral at physiologic pH to reduce systemic toxicity. Helper phospholipids support the lipid bilayer, and cholesterol regulates stability, fluidity, and membrane fusion. PEGylated lipids improve colloidal stability and prevent rapid clearance by the immune system. LNP-mediated mRNA uptake by cells primarily occurs via macropinocytosis and clathrin-mediated endocytosis, followed by endosomal escape to the cytoplasm for translation [96,97].

Anionic mRNA lipoplexes

mRNA lipoplexes (RNA–LPXs) are engineered nanoparticles designed to target DCs in secondary lymphoid organs, such as the spleen and lymph nodes, by leveraging innate antiviral immune pathways. RNA–LPXs typically carry a net negative charge, enabling efficient uptake by DCs via macropinocytosis without the need for additional ligand modifications [96,97]. Once internalized, they activate type I interferon

(IFN-α) signaling, thereby promoting antigen presentation, costimulation, and robust antigen-specific T cell expansion. Representative RNA–LPX-based vaccines include BioNTech's BNT111 (FixVac, a fixed-antigen vaccine targeting shared TAAs) [54] and BNT122 (iNeST, a personalized cancer vaccine encoding patient-specific neoantigens) [40,98].

Multilamellar mRNA–lipid particle aggregates

LPAs are multilayered "onion-like" RNA-lipid aggregates designed to enhance the antigen loading and immunogenicity of tumor mRNA antigens markedly [56]. In contrast to typical LNP designs that rely on TLR engagement in immune cells, RNA–LPAs activate RIG-I in stromal cells, leading to a massive cytokine/chemokine response, immune cell trafficking, and potent anticancer immunity. Preclinical and early human trials in GBM showed promising results, including improved survival and tumor microenvironment (TME) reprogramming [56].

Protamine–mRNA complexes

Protamine, one of the earliest clinically tested mRNA vaccine carriers, forms electrostatic complexes that protect mRNA from degradation and activate innate immunity. CureVac's RNActive® platform advanced this strategy by pairing protamine with sequence-optimized mRNA to enhance expression and immunogenicity [99]. Protamine-based vaccines, such as CV9104 (prostate cancer) [100] and CV9202 (NSCLC, NCT01915524) [101–103], showed good tolerability and immune activation in clinical trials but limited therapeutic benefit. Although protamine laid important groundwork for mRNA vaccine development, challenges in consistency and tolerability have driven a shift toward LNPs, nowadays the dominant and clinically approved mRNA delivery platform.

Virus-like particles

Virus-like particles (VLPs) are self-assembling nanostructures that mimic viral architecture to encapsulate and deliver mRNA efficiently, offering the delivery advantages of viruses without the risks of replication or genomic integration. A key innovation is DC-targeting VLPs (DVLPs) [104], which use engineered Sindbis virus glycoproteins to deliver mRNA to DC-SIGN–expressing DCs selectively, eliciting potent, durable T and B cell responses. Compared with lipid nanoparticles and nontargeted VLPs, DVLPs show superior lymphoid organ targeting and immunogenicity, maintaining VLPs' safety. Additionally, mRNA-carrying lentiviral particles (mLP-CRISPR) [105] and programmable ribonucleoprotein delivery VLPs (RIDE) [106] have been developed for Cas9/gRNA delivery, enabling efficient, tissue-specific gene editing without immunotoxicity across multiple disease models. Endogenous protein–based platforms, such as PEG10-VLPs [107], further improve tolerability. Together, these innovations position VLPs, particularly DC-targeted variants, as scalable, safe, and highly immunogenic vectors for mRNA-based antitumor and gene-editing therapies.

Cell-based delivery systems

RNA-loaded DC vaccines represent a personalized immunotherapeutic strategy whereby autologous DCs are transfected *ex vivo* with mRNA encoding TAAs. In this approach, mRNA is most commonly introduced via electroporation and bypasses the delivery barriers associated with *in vivo* administration [18]. Once loaded, these DCs translate mRNA into full-length proteins, process them, and present the resulting epitopes on MHC class I and II molecules, leading to the activation of antigen-specific T cells. Clinical trials have confirmed their safety and immunogenicity across malignancies, such as acute myeloid leukemia (AML) [108,109], melanoma [29], GBM [110], and prostate cancer [111]. Nonetheless, this approach remains limited by complex manufacturing, suboptimal lymph node homing, and variable clinical efficacy [18,97]. As a result, the field is gradually shifting toward *in vivo* mRNA vaccine platforms, although RNA-loaded DCs continue to offer distinct advantages for personalized multiepitope vaccine development, particularly in low-immunogenic or antigen-sparse tumors [34,40].

Mechanisms of mRNA vaccines in cancer immunotherapy

The application of mRNA technology has evolved beyond its initial focus on infectious diseases to address complex conditions like cancer [14–16,112]. This shift is largely driven by its inherent flexibility, favorable safety profile, and rapid adaptability, characteristics that make it particularly suitable for personalized cancer immuno-therapy. In this context, mRNA-based therapeutics have shown great promise in cancer vaccines [95,113]; therapies involving cytokines [25] or other immune-stimulatory molecules; and adoptive T cell therapies, such as CAR-T and TCR-T [34].

These vaccines activate antitumor immunity by encoding tumor antigens processed via MHC pathways, eliciting cellular and humoral responses. Compared with conventional cancer treatments, mRNA approaches offer high efficacy, low toxicity with generally manageable and transient adverse events, rapid manufacturing, and safe

administration. Additionally, mRNA does not integrate into the host genome, thus eliminating the risk of insertional mutagenesis. However, challenges, such as stability, delivery efficiency, and immune modulation, remain. Notably, personalized mRNA vaccines targeting neoantigens in tumors, such as melanoma and pancreatic cancer, are especially promising, showing strong immunogenicity and encouraging clinical responses.

Targeting tumor antigens: TAAs and TSAs

Cancer vaccines aim to induce or enhance antitumor immunity by stimulating the immune system with specific tumor antigens, which are broadly categorized as TAAs and TSAs [22–24]. TAAs and TSAs serve as critical targets for the development of cancer vaccines and other immunotherapeutic approaches.

TAAs

TAAs are typically self-antigens that are overexpressed in tumor cells but are also present in some normal cells, often at low levels [13,114]. However, because TAAs are present in normal tissues, the host immune system often exhibits tolerance to them, limiting efficacy and immunogenicity while also posing a risk of on-target/off-tumor toxicity of TAA-targeted therapies [113]. Several TAA mRNA vaccines have entered clinical evaluation. BNT111 (BioNTech), which encodes four melanoma-associated antigens (NY-ESO-1, Tyrosinase, MAGE-A3, and TPTE), is currently in phase 2 trials and has demonstrated robust T cell responses and clinical benefit in advanced melanoma [54]. CV9103 (CureVac) is a protamine-stabilized mRNA vaccine encoding four prostate cancer antigens (PSA, PSMA, PSCA, and STEAP1) and has been primarily assessed for safety and immunogenicity [115]. Similarly, RNA-Mel-03 (CureVac), targeting six melanoma-associated antigens (Melan-A, Tyrosinase, gp100, Mage-A1, Mage-A3, and Survivin), has shown a favorable safety profile in early-stage clinical studies [116].

TSAs

TSAs, also known as neoantigens, are uniquely expressed by tumor cells and absent in normal tissues. They typically arise from various genomic alterations, such as single-nucleotide variants, insertions/deletions (indels), and aberrant translation events [113,117]. As “nonself” antigens, TSAs tend to exhibit high tumor specificity and immunogenicity, thereby overcoming the central tolerance limitations faced by self-antigens and making them highly attractive targets for cancer immunotherapy [118]. While many neoantigens are patient specific, some hotspot mutations in KRAS [119–121] or TP53 [120,122] are recurrent across patients and cancer types, providing opportunities for the development of fixed, “off-the-shelf” vaccines. By contrast, personalized cancer vaccines, such as BNT122 (BioNTech, which includes up to 20 neoantigens) [39,40,98] and mRNA-4157 (Moderna, which incorporates up to 34 neoantigens) [123–125], are being explored to deliver multiple patient-specific TSAs, thereby broadening immune coverage and enhancing therapeutic efficacy. Beyond classical ORF-derived neoantigens, recent research has expanded the TSA landscape to include noncanonical sources, such as gene fusions, aberrant splicing events, transposable elements, noncanonical ORFs, and noncoding regions, some of which can be shared across multiple tumor types [22,37,38,117,126]. Notably, gene fusions represent a valuable source of TSAs by generating novel ORFs through chromosomal rearrangements, often producing unique peptides spanning fusion breakpoints that are absent in normal tissues and highly immunogenic. Their recurrence and shared nature across patients make them attractive candidates for “off-the-shelf” cancer vaccines and engineered T cell therapies [126–129]. Together, these advances underscore the growing diversity and therapeutic potential of TSAs in next-generation cancer immunotherapy.

Encoding immunomodulatory molecules: cytokines, adjuvants, and STING agonists

Beyond directly encoding tumor antigens, mRNA technology is increasingly employed to encode immunomodulatory molecules that shape the immune response and enhance antitumor activity.

Cytokines

The intratumoral injection of cytokine-encoding mRNA is a key strategy to remodel the TME by achieving high local protein concentrations while avoiding systemic toxicities [26–28,130]. Clinical trials are testing this approach in various solid tumors and lymphomas, primarily using two strategies: multicytokine cocktails or single-agent immunomodulators. For example, the cocktail therapy BNT131 (SAR441000; NCT03871348) [131] delivers four distinct cytokines (IL-12, IFN-α, GM-CSF, and IL-15 sushi) to remodel an immunologically cold TME into an immunogenic state comprehensively. Similarly, mRNA-2752 (NCT03739931 and NCT02872025) [27] combines OX40L with IL-23 and IL-36γ to activate immunity in patients with solid tumors and lymphomas synergistically. Conversely, single-agent strategies focus on one potent molecule. The mRNA-2416 (NCT03323398) [26] trial, for instance, uses intratumoral OX40L mRNA in patients with melanoma and other advanced cancers to reinvigorate exhausted T

cells locally. Other targeted approaches in clinical testing for various solid tumors include mRNAs encoding potent single cytokines, such as IL-12 (MEDI1191; NCT03946800) [28], IL-7/IL-2 (BNT152 + BNT153; NCT04710043), and optimized IL-2 (BNT151; NCT04455620).

Adjuvants

mRNA can also be used to encode adjuvants, boosting the magnitude of immune responses. While mRNA itself possesses intrinsic adjuvant activity by engaging pattern recognition receptors, such as TLRs and RIG-I, the strategy of encoding specific immune-activating proteins serves as a powerful approach to enhance immunogenicity further. The TriMix combination (a cocktail of mRNAs encoding CD70, CD40L, and constitutively active TLR4 [caTLR4]) has been shown to promote DC maturation effectively and elicit strong cytotoxic T lymphocyte (CTL) responses [29,30]. GM-CSF, mentioned earlier as a cytokine, can also function as an adjuvant by supporting DC recruitment, expansion, and cross-presentation, particularly when co-delivered with antigen-encoding mRNA vaccines [132]. Moreover, the combination of BCMA–mRNA lipid LNPs with poly(I:C), a synthetic TLR3 agonist, has been reported to amplify BCMA-specific immune responses further and enhance antitumor efficacy [133].

Agonists of stimulator of interferon genes

The stimulator of interferon genes (STING) pathway is pivotal for linking innate and adaptive immunity through type I interferon production. The codelivery of a STING agonist (cGAMP) with mutant KRAS mRNA has shown synergistic antitumor effects in pancreatic cancer models by inducing type I interferon responses and activating cytotoxic CD8 T cells. This simultaneous delivery of "what to target" (antigen) and "how to activate" (adjuvant) within the same delivery system is key to generating robust and effective antitumor immune responses, particularly in immunologically cold tumors [134]. Another mRNA-encoded adjuvant STING^{V155M} enhances antigen-specific CD8 T cell responses, thereby improving the efficacy of mRNA vaccines [31].

mRNA for cell engineering: CAR-T or TCR-T for adoptive cell therapy

mRNA-based CAR-T and TCR-T cell therapies represent a nonviral, transient alternative to conventional gene-modified T cell approaches. Instead of using viral vectors to integrate CAR or TCR genes into T cells stably, synthetic mRNA encoding these receptors is delivered to cells, allowing temporary expression without genomic integration [18,34,95]. This approach offers a flexible, nonintegrating, and potentially highly safe platform for T cell engineering and holds promise in combination with mRNA cancer vaccines to potentiate antitumor immunity.

Two main strategies are available, as detailed below:

- ***In vitro* mRNA transfection** T cells isolated from patients or healthy donors are transfected *ex vivo* with mRNA encoding CAR or TCR molecules, commonly via electroporation or lipid-based carriers [35,36]. Clinical trials have evaluated *ex vivo* mRNA-transfected CAR-T cells targeting antigens, such as mesothelin [135] and c-Met [136], and the results of these trials have shown early signs of safety and efficacy.
- ***In vivo* mRNA delivery** Emerging approaches aim to deliver CAR/TCR mRNA directly into patients using targeted LNPs (tLNPs) to address the complexity and high cost of *ex vivo* manufacturing. These nanoparticles are engineered to transfect circulating T cells, enabling the *in vivo* generation of CAR- or TCR-T cells [137]. By incorporating cell-specific antibodies (e.g., anti-CD5 for T cells), tLNPs enable the efficient *in vivo* delivery of mRNA payloads to specific cell types, allowing precise immune cell engineering within the body [138]. A recent preclinical study has demonstrated that tLNP-mediated *in vivo* CAR-T cells successfully depleted B cells and induced immune reset, with reconstituted B cells being predominantly naïve, offering a scalable, safer, and more accessible alternative to conventional *ex vivo* CAR-T therapies [139]. While still primarily at the preclinical stage, this approach holds promise for simplifying and broadening access to T cell therapies.

Additional applications include the following:

- **Genome editing of T cells using mRNA** mRNA can be used to express genome-editing tools (e.g., CRISPR-Cas9) in T cells transiently, enabling targeted gene knockouts (e.g., PD1 or endogenous TCRs) to enhance antitumor function or support allogeneic use [32,33].
- **Combining mRNA vaccines with conventional CAR-T** Some strategies combine traditional CAR-T cells (produced with viral vectors) with mRNA vaccines that encode the target antigen. For example, in the BNT211 (BioNTech; NCT04503278) trial, CLDN6 CAR-T cells were coadministered with an mRNA vaccine (CARVac) encoding CLDN6 to boost *in vivo* CAR-T cell expansion and persistence [57].
- **pMHC binder design** Traditional CAR-T therapies are limited to targeting surface antigens, whereas many TSAs are intracellular and presented via peptide–MHC complexes (pMHCs), which are critical for CD8 T cell–mediated immune surveillance. Natural T cell receptors (TCRs) can recognize pMHCs but face challenges in clinical application because of low affinity, recognition complexity, and potential off-target risks from cross-reactivity. Leveraging advanced generative protein design tools, such as RFdiffusion [140] and

ProteinMPNN [141], in combination with AlphaFold2/3 [142] for structural prediction enables the *de novo* design of minibinder and TCR mimics that specifically bind to tumor-associated pMHCs [143–145]. These designed binders exhibit high affinity and specificity for pMHC-I complexes. For instance, the lead candidate NY1-B04 targets the NY-ESO-1 antigen presented by HLA-A*02:01 with a dissociation constant of 6.92 nmol/L [144]. As a TAA, NY-ESO-1 is widely expressed across multiple tumors but rarely in normal tissues, making it a promising target for "off-the-shelf" CAR designs. These binders hold considerable promise for applications in cellular therapies, particularly through their integration into CARs. Such CAR-integrated binders can effectively induce the killing of NY-ESO-1 melanoma cells *in vitro*. Moreover, this strategy has also been extended to design binders targeting neoantigen pMHCs (e.g., RVTDESILSY/HLA-A*01:01) [144], underscoring the potential of this platform for universal and personalized T cell–based immunotherapies.

Role of immune cells in antitumor immunity

Effective antitumor immunity induced by mRNA vaccines depends on the coordinated activation of multiple immune cell populations, each playing distinct but complementary roles (Fig. 3). The success of mRNA vaccine strategies hinges not only on the efficient

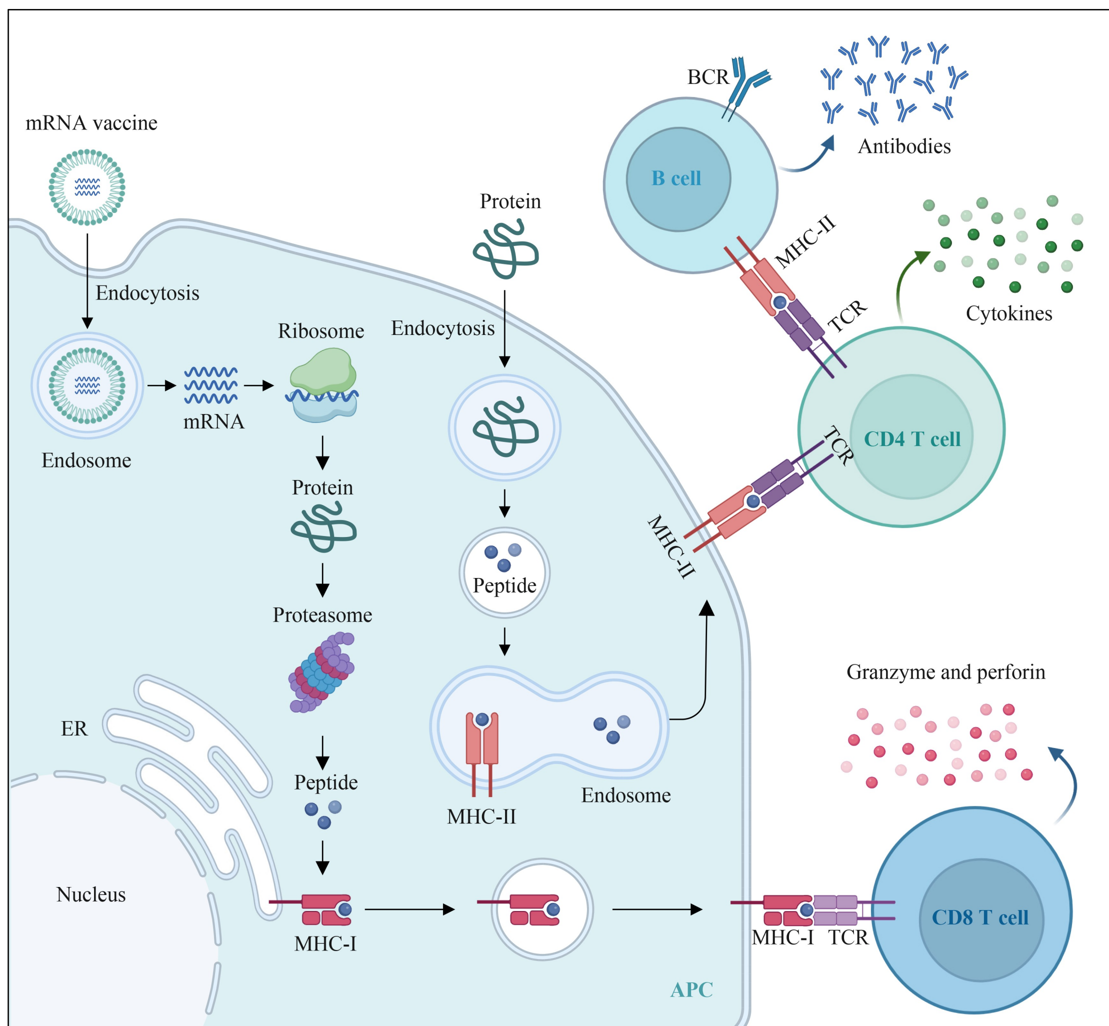

Fig. 3 Mechanism of immune activation by mRNA vaccines. After administration, mRNA is taken up by antigen-presenting cells (APCs) through endocytosis and released into the cytosol, where it is translated into antigenic proteins. These intracellular proteins are degraded by the proteasome and presented on MHC-I molecules to activate cytotoxic CD8 T cells, which eliminate target cells by releasing granzyme and perforin. In parallel, secreted or extracellular proteins are processed in endosomes and presented on MHC-II molecules to activate CD4 helper T cells. These CD4 helper T cells enhance immune responses by promoting cytokine secretion and supporting B cell activation. Antigen-specific B cells internalize protein through the B cell receptor (BCR) and present peptides to CD4 T cells, which in turn provide help for antibody production. Together, mRNA vaccines stimulate cellular and humoral immunity through coordinated antigen presentation. This figure was created with BioRender.

intracellular delivery of the mRNA cargo but also on cell-type-specific targeting, particularly toward DCs, T cells, and B cells, to achieve comprehensive immune activation [146,147].

APCs

APCs, especially DCs, are the most potent initiators of adaptive immunity [97,148]. They play a critical role in capturing, processing, and presenting antigens via MHC class I and II molecules to activate CD8 and CD4 T cells, respectively. The abundance of DCs in the TME correlates with improved outcomes and responses to ICIs, such as anti-PD-1 [149,150]. The targeted *in vivo* delivery of mRNA to DCs using LNPs enhances antigen presentation and strengthens downstream T cell responses. Macrophages, another subset of APCs, also contribute by internalizing LNPs and translating the encoded mRNA, particularly in lymphoid tissues [96].

CD8 T cells

CD8 CTLs are the primary effectors responsible for directly killing tumor cells. Their abundance in tumors often correlates positively with response to ICIs and a favorable prognosis [151,152]. CTLs eliminate tumor cells through mechanisms, such as granule exocytosis (perforin and granzymes) and engagement of death receptors (Fas ligand) [113,153]. Eliciting a strong cytotoxic CD8 T cell response is crucial for eradicating cancerous cells in therapeutic cancer vaccines. However, chronic antigen exposure in the TME can lead to CD8 T cell exhaustion, compromising their ability to kill cancer cells [154,155].

CD4 T cells

CD4 T cells play multifaceted roles, providing critical help to CD8 T and B cells while also exhibiting direct cytotoxic activity in certain contexts [156]. They recognize MHC class II–presented peptides and support the development of high-affinity antibody responses. Interactions between antigen-specific CD4 T follicular helper cells and B cells in tertiary lymphoid structures (TLSs) further enhance the quality of adaptive immune responses [157]. Notably, mRNA–LNP vaccines have demonstrated the capacity to elicit strong CD4 T cell activation [158,159].

B cells

B cells, central to humoral immunity, not only produce antigen-specific antibodies but also act as professional APCs. They can process extracellular antigens and present them on MHC class II molecules to activate CD4 T cells [160]. Within the TME, TLS-associated B cells enhance antitumor immunity and support responses to checkpoint blockade [157,161]. mRNA delivery to B cells can amplify their antigen presentation capacity and promote the generation of neoantigen-specific antibodies with therapeutic potential [162].

Clinical applications of mRNA vaccines across cancer types

The success of mRNA vaccine technology has spurred numerous clinical trials investigating its application in various cancer diagnoses as monotherapy and, increasingly, in combination with ICIs. These trials provide concrete evidence of mRNA's potential in oncology. The positive results of clinical trials provide strong clinical validation for the synergistic potential of combining personalized mRNA vaccines with ICIs, moving the field beyond preclinical promise to tangible patient benefit. mRNA-based immunotherapies are being actively explored across a broad spectrum of malignancies, showing promising efficacy, especially when combined with ICIs or conventional chemotherapy. Below is a summary of key clinical trials by cancer type (Tables 3 and 4).

Melanoma

mRNA vaccines have demonstrated the most advanced clinical progress in the treatment of melanoma. Multiple mRNA vaccine strategies, including lipoplex formulations and DC platforms, have shown promising immunogenicity and clinical activity. BNT111 (encoding four TAAs; NCT02410733) [54] showed a favorable safety profile and induced durable responses when combined with PD-1 blockade in resistant patients during a phase I trial and is now being evaluated in a global phase II trial (NCT04526899) to assess its clinical efficacy further. Personalized neoantigen mRNA vaccines, such as BNT121 (IVAC MUTANOME; NCT02035956) [167], BNT122 (iNeST; NCT03815058), and mRNA-4157 (V940; NCT03897881) [123], have elicited robust immunogenicity and neoantigen-specific T cell responses. The phase IIb KEYNOTE-942 trial demonstrated that mRNA-4157 (V940) combined with pembrolizumab substantially improved 18-month recurrence-free survival compared with pembrolizumab alone (79% vs. 62%) [123]. Building upon these results, a phase III double-blind randomized trial (NCT05933577) is currently ongoing to evaluate pembrolizumab plus mRNA-4157 versus pembrolizumab alone in patients with resected high-risk stage II–IV melanoma [55]. This study aims to enroll approximately 1,089 participants, with recurrence-free survival as the primary endpoint. According to the latest update, the trial is actively

Table 3 Clinical trials for mRNA cancer vaccines

Identifier	Status	Phase	mRNA drug	Cancer type	Antigen (number)	Delivery	Administration route	Target antigen details	Combination	Sponsor
NCT03394937 [163]	Terminated	Phase 1	ECI-006	Melanoma	TAA (5)	Naked	Intranodal	CD40L, CD70, caTLR4; tyrosinase, gp100, MAGE-A3, MAGE-C2, and PRAME	None	eTheRNA immunotherapies
NCT01684241	Completed	Phase 1	RBL001/RBL002	Melanoma	TAA (2)	Naked	Intranodal	NY-ESO-1, tyrosinase	None	BioNTech
NCT02410733 [54]	Completed	Phase 1	BNT111	Melanoma	TAA (4)	LPX	Intravenous	NY-ESO-1, tyrosinase, MAGE-A3, and TPTE	With or without standard PD-1 therapy	BioNTech
NCT04526899	Active, not recruiting	Phase 2	BNT111	Melanoma	TAA (4)	LPX	Intravenous	NY-ESO-1, tyrosinase, MAGE-A3, and TPTE	With cemiplimab	BioNTech
NCT04382898 [164]	Terminated	Phase 1/2	BNT112	Prostate	TAA (5)	LPX	Intravenous	PAP, PSA/KLK3, KLK2, HOXB13, and NKX3-1	With cemiplimab	BioNTech
NCT03418480	Completed	Phase 1/2	BNT113	Head and neck	Viral TAA (2)	LPX	Intradermal	HPV16 E6 and E7 oncoproteins	With anti-CD40 antibodies	University of Southampton
NCT04534205	Recruiting	Phase 2/3	BNT113	Head and neck	Viral TAA (2)	LPX	Intravenous	HPV16 E6 and E7 oncoproteins	With pembrolizumab	BioNTech
NCT04163094	Terminated	Phase 1	BNT115	Ovarian	TAA (3)	LPX	Intravenous	Ovarian cancer tumor–associated antigens	With carboplatin plus paclitaxel	University Medical Center Groningen
NCT02316457 [165]	Completed	Phase 1	BNT114 + BNT122	Breast	TAA (3, 4); Personalized NA (20)	LPX	Intravenous	Personalized cancer vaccine encoding individual tumor mutations	None	BioNTech
NCT05142189 [166]	Recruiting	Phase 1	BNT116	Lung	TAA (6)	LPX	Intravenous	NSCLS tumor–associated antigens	With cemiplimab plus docetaxel	BioNTech
NCT02035956 [167]	Completed	Phase 1	BNT121	Melanoma	TAA (2); Personalized NA (10)	Naked	Intranodal	NY-ESO-1, tyrosinase; 10 selected neoepitopes for each patient	None	BioNTech
NCT03815058	Completed	Phase 2	BNT122	Melanoma	NA (20)	LPX	Intravenous	Personalized cancer vaccine encoding individual tumor mutations	With pembrolizumab	Genentech
NCT03289962 [39]	Active, not recruiting	Phase 1	BNT122	Solid tumors	NA (20)	LPX	Intravenous	Personalized cancer vaccine encoding individual tumor mutations	With atezolizumab	Genentech
NCT04486378 [168]	Recruiting	Phase 2	BNT122	Colorectal	NA (20)	LPX	Intravenous	Personalized cancer vaccine encoding individual tumor mutations	None	BioNTech

(*Continued*)

Identifier	Status	Phase	mRNA drug	Cancer type	Antigen (number)	Delivery	Administration route	Target antigen details	Combination	Sponsor
NCT04161755 [40,98]	Active, not recruiting	Phase 1	BNT122	Pancreas	NA (20)	LPX	Intravenous	Personalized cancer vaccine encoding individual tumor mutations	With atezolizumab plus mFOLFIRINOX	BioNTech + Memorial Sloan Kettering Cancer Center
NCT05968326	Recruiting	Phase 2	BNT122	Pancreas	NA (20)	LPX	Intravenous	Personalized cancer vaccine encoding individual tumor mutations	With atezolizumab plus mFOLFIRINOX	BioNTech + Genentech
NCT06534983	Recruiting	Phase 2	BNT122	MIUC	NA (20)	LPX	Intravenous	Personalized cancer vaccine encoding individual tumor mutations	With nivolumab	BioNTech + Roche
NCT04267237	Withdrawn	Phase 2	BNT122	Lung	NA (20)	LPX	Intravenous	Personalized cancer vaccine encoding individual tumor mutations	With atezolizumab	BioNTech + Roche
NCT04683939 [169]	Terminated	Phase 1/2	BNT141	Solid tumors	TAA (1 [CLDN18.2])	LNP	Intravenous	CLDN18.2	With gemcitabine	BioNTech
NCT05262530 [170,171]	Recruiting	Phase 1/2	BNT142	Solid tumors	TAA (2 [CD3, CLDN6])	LNP	Intravenous	CD3xCLDN6	None	BioNTech
NCT03871348 [131]	Terminated	Phase 1	BNT131	Solid tumors	Cytokine (4)	LNP	Intratumoral	IL-12, IFN-α 2b, GM-CSF, and IL-15sushi	With cemiplimab	BioNTech + Sanofi
NCT04455620	Terminated	Phase 1/2	BNT151	Solid tumors	Cytokine (1)	LNP	Intravenous	Optimized IL-2	None	BioNTech
NCT04710043	Active, not recruiting	Phase 1	BNT152 + BNT153	Solid tumors	Cytokine (2)	LNP	Intravenous	IL-7, IL-2	None	BioNTech
NCT04503278 [57,171,172]	Recruiting	Phase 1/2	BNT211	Solid tumors	TAA (1 [CLDN6])	LPX	Intravenous	CLDN6 (CARVac)	With CLDN6 CAR-T cells	BioNTech + Gene Therapies
NCT00906243 [115]	Terminated	Phase 1/2	CV9103	Prostate	TAA (4)	Protamine	Intradermal	PSA, PSMA, PSCA, and STEAP1	None	CureVac + University of Florida
NCT00831467 [115]	Completed	Phase 1/2	CV9103	Prostate	TAA (4)	Protamine	Intradermal	PSA, PSMA, PSCA, and STEAP1	None	CureVac + University of Florida
NCT02140138	Terminated	Phase 2	CV9104	Prostate	TAA (6)	Protamine	Intradermal	PSA, PSMA, PSCA, STEAP1, PAP, and MUC1	None	CureVac
NCT01817738 [100]	Terminated	Phase 1/2	CV9104	Prostate	TAA (6)	Protamine	Intradermal	PSA, PSMA, PSCA, STEAP1, PAP, and MUC1	None	CureVac
NCT00923312 [115]	Completed	Phase 1/2	CV9201	Lung	TAA (5)	Protamine	Intradermal	MAGE-C1, MAGE-C2, NY-ESO-1, Survivin, and 5T4	None	CureVac

(*Continued*)

Identifier	Status	Phase	mRNA drug	Cancer type	Antigen (number)	Delivery	Administration route	Target antigen details	Combination	Sponsor
NCT01915524 [101,102]	Terminated	Phase 1	CV9202	Lung	TAA (6)	Protamine	Intradermal	MAGE-C1, MAGE-C2, NY-ESO-1, Survivin, 5T4, and MUC-1	With local irradiation	CureVac
NCT03164772 [103]	Completed	Phase 1/2	CV9202	Lung	TAA (6)	Protamine	Intradermal	NY-ESO-1, MAGE-C1, MAGE-C2, TPBG, and MUC1	With durvalumab+/−tremelimumab	CureVac + Ludwig Institute for Cancer Research
NCT00204607 [116]	Completed	Phase 1/2	RNA-Mel-03	Melanoma	TAA (6)	Protamine	Intradermal	Melan-A, Tyrosinase, gp100, Mage-A1, Mage-A3, and Survivin	With GM-CSF	CureVac + University Hospital Tuebingen
NCT00204516 [173]	Completed	Phase 1/2	RNA-Mel-03	Melanoma	TAA (6)	Naked	Intradermal	Melan-A, Tyrosinase, gp100, Mage-A1, Mage-A3, and Survivin	With GM-CSF	CureVac + University Hospital Tuebingen
NCT05938387 [174]	Active, not recruiting	Phase 1	CVGBMM	GBM	TAA (8)	LNP	Intramuscular	na	None	CureVac
NCT03480152 [120]	Terminated	Phase 1/2	NCI-4650	Solid tumors	Driver NA (3) + Personalized NA (15)	LNP	Intramuscular	TP53, KRAS, or PIK3CA driver genes; 15 *in silico*–predicted HLA-I potential neoantigens	None	Moderna + National Cancer Institute
NCT05533697 [175,176]	Recruiting	Phase 1/2	mRNA-4359	Solid tumors	TAA (2 [PD-L1, IDO])	LNP	Intramuscular	PD-L1 and IDO	With pembrolizumab	Moderna
NCT03313778 [124,125]	Recruiting	Phase 1	mRNA-4157	Solid tumors	NA (34)	LNP	Intramuscular	Personalized cancer vaccine encoding 34 neoantigens	With pembrolizumab	Moderna
NCT03897881 [123]	Recruiting	Phase 2	mRNA-4157	Melanoma	NA (34)	LNP	Intramuscular	Personalized cancer vaccine encoding 34 neoantigens	With pembrolizumab	Moderna
NCT05933577 [55]	Active, not recruiting	Phase 3	mRNA-4157	Melanoma	NA (34)	LNP	Intramuscular	Personalized cancer vaccine encoding 34 neoantigens	With pembrolizumab	Moderna + Merck Sharp & Dohme
NCT06077760 [177]	Recruiting	Phase 3	mRNA-4157	Lung	NA (34)	LNP	Intramuscular	Personalized cancer vaccine encoding 34 neoantigens	With pembrolizumab	Moderna + Merck Sharp & Dohme
NCT03948763	Terminated	Phase 1	mRNA-5671	Lung, colon, pancreas	Driver NA (4)	LNP	Intramuscular	KRAS (G12C, G12D, G12V, and G13D)	With pembrolizumab	Moderna + Merck
NCT05456165	Terminated	Phase 2	GRT-C901 + GRT-R902	Colorectal	Personalized NA (20)	ChAd68 + saRNA	Intramuscular	Shared neoantigen	With atezolizumab plus ipilimumab	Gritstone
NCT05141721 [178]	Active, not recruiting	Phase 2/3	GRT-C901 + GRT-R902	Colorectal	Personalized NA (20)	ChAd68 + saRNA	Intramuscular	Shared neoantigen	With atezolizumab plus ipilimumab	Gritstone
NCT03639714 [179]	Completed	Phase 1/2	GRT-C901 + GRT-R902	Solid tumors	Personalized NA (20)	ChAd68 + saRNA	Intramuscular	Shared neoantigen	With nivolumab plus ipilimumab	Gritstone

(*Continued*)

Identifier	Status	Phase	mRNA drug	Cancer type	Antigen (number)	Delivery	Administration route	Target antigen details	Combination	Sponsor
NCT03953235 [180]	Completed	Phase 1/2	GRT-C903 + GRT-R904	Solid tumors	Personalized NA (20)	ChAd68 + saRNA	Intramuscular	Shared neoantigen: KRAS, TP53, β-catenin, and BRAF	With nivolumab plus ipilimumab	Gritstone
NCT05761717	Not yet recruiting	Phase 1	na	Liver	TAA (1)	na	Subcutaneous	na	With stintilimab	Shanghai Zhongshan Hospital
NCT05227378	Not yet recruiting	Phase 1	na	Gastric	NA (na)	na	Not described	Neoantigen tumor vaccine	With or without PD-1/L1	Peking University Cancer Hospital
NCT06141369	Recruiting	Phase 1	mRNA-0523-L001	Endocrine tumors	NA (na)	na	Intramuscular	Individualized neoantigen vaccine	None	Shanghai Jiao Tong University
NCT06156267	Not yet recruiting	Phase 1	PANC-IIT-RGL	Pancreas	NA (na)	na	Not described	Personalized cancer vaccine encoding individual tumor mutations	With adebrelimab	Fudan University
NCT05264974 [181]	Suspended	Phase 1	na	Melanoma	Autologous tumor RNA	LPA	Intravenous	Autologous tumor RNA	None	University of Florida
NCT05660408 [181]	Recruiting	Phase 1/2	na	Sarcoma	Autologous tumor RNA	LPA	Intravenous	Autologous tumor RNA	None	University of Florida
NCT04573140 [56,181]	Recruiting	Phase 1	na	GBM	TAA (1); Autologous tumor RNA	LPA	Intravenous	Formulation with pp65 LAMP and autologous tumor mRNA	None	University of Florida
NCT06389591 [181]	Recruiting	Phase 1	na	GBM	TTRNA	LPA	Intravenous	TTRNA	None	University of Florida
NCT05738447	Recruiting	Phase 1	WGc-0201	Liver	Viral (na)	na	Intramuscular	HBV virus	None	West China Hospital
NCT05714748 [182]	Recruiting	Phase 1	WGc-043	Solid tumors	Viral (na)	na	Intramuscular	EBV virus	None	West China Hospital
NCT05202561	Unknown	Phase 1	LWY21084CBY	Solid tumors	Driver NA (1 [KRAS])	na	Intramuscular	KRAS (G12C, G12D, and G12V)	With or without navuliumab	The First Affiliated Hospital of BenGBMu Medical University
NCT05916248	Recruiting	Phase 1	mRNA-0217/S001	Solid tumors	Personalized NA (1–20)	LNP	Intramuscular	Personalized cancer vaccine encoding individual tumor mutations	With pembrolizumab	Ruijin Hospital
NCT05916261	Recruiting	Phase 1	mRNA-0217/S001	Pancreas	Personalized NA (na)	LNP	Intramuscular	na	With pabolizumab	Ruijin Hospital
NCT06496373	Recruiting	Early Phase 1	XP-004	Pancreas	Personalized NA (1–20)	LNP	Intramuscular	KRAS (G12D, G12V, G12R, and G12C); Personalized neoantigen tumor vaccine	With toripalimab	Ruijin Hospital

(*Continued*)

Identifier	Status	Phase	mRNA drug	Cancer type	Antigen (number)	Delivery	Administration route	Target antigen details	Combination	Sponsor
NCT06577532	Recruiting	Early Phase 1	ABO2102	Pancreas	Driver NA (1 [KRAS])	LNP	Intramuscular	KRAS (G12A, G12C, G12D, G12V, and G13D)	With toripalimab	Ruijin Hospital
NCT03946800 [183]	Completed	Phase 1	MEDI1191	Solid tumors	Cytokine (1)	LNP	Intratumoral	IL-12	With durvalumab	MedImmune LLC
NCT03739931 [184]	Active, not recruiting	Phase 1	mRNA-2752	Solid tumors	Cytokine (3)	LNP	Intratumoral	Human OX40L, IL-23, and IL-36γ	With durvalumab	ModernaTX, Inc.
NCT02872025 [27]	Active, not recruiting	Early Phase 1	mRNA-2752	Breast Cancer	Cytokine (3)	LNP	Not described	Human OX40L, IL-23, and IL-36γ	With pembrolizumab	ModernaTX, Inc.L3:L66

Search criteria: Keywords "cancer" + "RNA vaccine" on https://clinicaltrials.gov/ on May 30, 2025; additional trials added based on PubMed search; CLDN, claudin; GBM, glioblastoma; NA, neoantigens; na, not available; PAP, prostatic acid phosphatase; TAA, tumor-associated antigens; LNP, lipid nanoparticle; LPX, lipoplex; ChAd68, chimp adenovirus; saRNA, self-amplifying mRNA; LPA, lipid particle aggregates; MIUC, muscle invasive urothelial carcinoma; TTRNA, total tumor RNA.

Table 4 Clinical trials for mRNA-load dendritic cell cancer vaccines

Identifier	Status	Phase	Cancer type	Antigen (number)	Administration route	Target antigen	Combination	Sponsor
NCT05000801	Recruiting	Not applicable	AML	TAA (3)	Not described	WT1, hTERT, and Survivin	With follow-up care	Hospital Affiliated to Academy of Military Medical Sciences
NCT00834002 [185]	Completed	Phase 1	AML	TAA (1)	Intradermal	WT1	None	University Hospital, Antwerp
NCT00965224 [186]	Completed	Phase 2	AML	TAA (1)	Not described	WT1	With standard therapy	Zwi Berneman
NCT01686334	Active, not recruiting	Phase 2	AML	TAA (1)	Intradermal	WT1	With follow-up care	Zwi Berneman
NCT00510133 [108]	Completed	Phase 2	AML	TAA (1)	Not described	hTERT, LAMP	None	Asterias Biotherapeutics, Inc.
NCT00514189	Terminated	Phase 1	AML	Autologous tumor RNA	Intranodal	AML mRNA plus lysate	None	M.D. Anderson Cancer Center
NCT03083054	Unknown	Phase 1/2	AML, MDS	TAA (1)	Not described	WT1	None	University of Campinas, Brazil
NCT03396575	Terminated	Phase 1	Brainstem gliomas	TTRNA	Intradermal	TTRNA	With temozolomide	University of Florida
NCT00003432	Terminated	Phase 1/2	Breast	TAA (1)	Intravenous	CEA	None	Duke University
NCT06530082	Not yet recruiting	Phase 1	Breast	NA (1)	Intradermal	CircFAM53B-219aa	With camrelizumab	Sun Yat-Sen Memorial Hospital
NCT00003433	Completed	Phase 1/2	Colorectal	TAA (1)	Intravenous	CEA	None	Duke Cancer Institute
NCT00228189 [187]	Completed	Phase 1/2	Colorectal, Liver	TAA (1)	Not described	CEA	None	Radboud University Medical Center
NCT04911621 [188]	Active, not recruiting	Phase 1/2	DIPG	TAA (1)	Intradermal	WT1	With chemoradiation	University Hospital, Antwerp

(*Continued*)

Identifier	Status	Phase	Cancer type	Antigen (number)	Administration route	Target antigen	Combination	Sponsor
NCT04837547	Recruiting	Phase 1	DIPG	TTRNA	Not described	TTRNA	With TTRNA-xALT, autologous HSCs	University of Florida
NCT02649582	Active, not recruiting	Phase 1/2	GBM	TAA (1)	Intradermal	WT1	With temozolomide	University Hospital, Antwerp
NCT00639639 [24,110,189]	Completed	Phase 1	GBM	TAA (1)	Intradermal	CMV pp65-LAMP	With autologous lymphocyte transfer and Td	Gary Archer Ph.D.
NCT02366728 [110]	Completed	Phase 2	GBM	TAA (1)	Intradermal	CMV pp65-LAMP	With temozolomide	Mustafa Khasraw, MBChB, MD, FRCP, FRACP
NCT03688178	Active, not recruiting	Phase 2	GBM	TAA (1)	Intradermal	CMV pp65-FILAMP	With temozolomide, varlilumab, and Td	Annick Desjardins, MD
NCT02465268 [190]	Completed	Phase 2	GBM	TAA (1)	Subcutaneous	CMV pp65-shLAMP or pp65-FILAMP	With temozolomide, GM-CSF, and Td	University of Florida
NCT04963413	Terminated	Phase 1	GBM	TAA (1)	Not described	CMV pp65-flLAMP	With GM-CSF	University of Florida
NCT03615404	Completed	Phase 1	GBM	TAA (1)	Not described	CMV pp65-flLAMP	With GM-CSF and Td	Gary Archer Ph.D.
NCT00626483 [191]	Completed	Phase 1	GBM	TAA (1)	Not described	CMV pp65-LAMP	With basiliximab	Gary Archer Ph.D.
NCT03548571 [192,193]	Recruiting	Phase 2/3	GBM	TAA (2); autologous tumor RNA	Intradermal	hTERT, Survivin, and autologous tumor stem cells	With temozolomide	Oslo University Hospital
NCT06514898	Recruiting	Phase 1	Medulloblastoma	TTRNA	Intradermal	TTRNA	With pembrolizumab	University of Florida
NCT01326104	Completed	Phase 1/2	Medulloblastoma	TTRNA	Intradermal	TTRNA	With TTRNA-xALT	University of Florida
NCT00005816	Completed	Phase 1	Kidney	Autologous tumor RNA	Intravenous; intradermal	Autologous tumor RNA	With conventional surgery	Duke University
NCT00006431 [194]	Unknown	Phase 1	Kidney	Autologous tumor RNA	Intravenous; intradermal	Autologous tumor RNA	None	National Center for Research Resources (NCRR)
NCT00087984	Completed	Phase 1/2	Kidney	Autologous tumor RNA	Not described	Autologous tumor RNA	None	Argos Therapeutics
NCT02170389	Terminated	Not Applicable	Kidney	TAA (1); autologous tumor RNA	Intradermal	Autologous tumor RNA/CD40L RNA	With nephrectomy	Roswell Park Cancer Institute
NCT00978913 [195]	Completed	Phase 1	Melanoma	TAA (3)	Intradermal	Survivin, hTERT, and p53	With cyclophosphamide	Inge Marie Svane
NCT00074230	Completed	Phase 1/2	Melanoma	TAA (3)	Subcutaneous	Melan-A, MAGE-3, and Survivin	None	University Hospital Erlangen (Erlangen, Germany)
NCT01456104 [196]	Completed	Phase 1	Melanoma	TAA (1)	Subcutaneous	Trp2	None	Memorial Sloan Kettering Cancer Center
NCT04335890 [197,198]	Unknown	Phase 1	Melanoma	Autologous tumor RNA; TAA (5)	Intravenous	Autologous tumor RNA; gp100, tyrosinase, PRAME, MAGE-A3, and IDO	With standard therapy	Hasumi International Research Foundation

(*Continued*)

Identifier	Status	Phase	Cancer type	Antigen (number)	Administration route	Target antigen	Combination	Sponsor
NCT00126685	Unknown	Phase 1/2	Melanoma	Autologous tumor RNA	Intradermal	Autologous tumor RNA	None	Dermatologische Klinik MIT Poliklinik-Universitaetsklinikum Erlangen
NCT01983748 [199]	Unknown	Phase 3	Melanoma	Autologous tumor RNA	Intravenous	Autologous tumor RNA	None	University Hospital Erlangen
NCT01216436	Terminated	Phase 1	Melanoma	TAA (4)	Intranodal	MART, tyrosinase, gp100, and MAGE-3	With GITRL/anti-CTLA4 RNA DC	Duke University
NCT00672542 [200]	Completed	Phase 1	Melanoma	TAA (4)	Intradermal	MART, tyrosinase, gp100, and MAGE-3	None	Scott Pruitt
NCT00243529 [201,202]	Completed	Phase 1/2	Melanoma	TAA (2)	Not described	gp100 and tyrosinase	None	Radboud University Medical Center
NCT01995708 [203]	Completed	Phase 1	Multiple myeloma	TAA (3)	Intradermal	CT7, MAGE-A3, and WT1	With standard treatment	Memorial Sloan Kettering Cancer Center
NCT04157127	Active, not recruiting	Phase 1	Pancreas	Autologous tumor RNA	Intradermal	Pancreatic adenocarcinoma mRNA and lysate	With standard therapy	Diakonos Oncology Corporation
NCT02649829 [204]	Completed	Phase 1/2	Pleural mesothelioma	TAA (1)	Intradermal	WT1	With standard therapy	University Hospital, Antwerp
NCT01197625 [111]	Active, not recruiting	Phase 1/2	Prostate	TAA (2); autologous tumor RNA	Not described	hTERT, Survivin, and mRNA from primary prostate cancer tissue	None	Oslo University Hospital
NCT00004211	Completed	Phase 1/2	Prostate	TAA (1)	Intravenous; intradermal	PSA	None	Duke University
NCT01153113	Withdrawn	Phase 1/2	Prostate	TAA (1)	Intradermal	hTERT and LAMP	None	University of Florida
NCT00010127	Terminated	Phase 1	Prostate	Autologous tumor RNA	Intradermal	Autologous tumor RNA	None	Duke University
NCT00108264	Completed	Phase 1	Prostate	Autologous tumor RNA	Not described	Autologous tumor RNA	None	US Department of Veterans Affairs
NCT00890032 [205]	Completed	Phase 1	Recurrent central nervous system neoplasm	Autologous tumor RNA	Intradermal	Autologous brain tumor stem cell mRNA	None	John Sampson
NCT03674073 [206]	Unknown	Phase 1	Liver	Personalized NA (30)	Not described	Personalized cancer vaccine encoding individual tumor mutations	With microwave ablation	Beijing Likang Life Science + Chinese PLA General Hospital
NCT06054932	Recruiting	Phase 1	Solid tumors	Personalized NA (10)	Not described	Personalized cancer vaccine encoding individual tumor mutations	None	Beijing Likang Life Science
NCT00004604	Completed	Phase 1	Solid tumors	TAA (1)	Intravenous	CEA	None	Duke University

Search criteria: Keywords "cancer" + "RNA vaccine" at the website of clinicaltrials.gov on May 30, 2025; additional trials added based on PubMed search; AML, acute myeloid leukemia; GBM, glioblastoma; hTERT, human telomerase reverse transcriptase; NA, neoantigens; na, not available; TAA, tumor-associated antigens; TTRNA, total tumor RNA; DIPG, diffuse intrinsic pontine glioma; MDS, myelodysplastic syndromes.

recruiting and is expected to be completed in 2029. DC-based vaccines (TriMixDC-MEL; NCT01302496), encoding CD70, CD40L, and TLR4, as well as the TAAs Tyrosinase, gp100, MAGE-A3, or MAGE-C2, also enhanced tumor-specific T cell responses when combined with ipilimumab in one phase II study, resulting in objective responses in 38% of patients with advanced melanoma [29].

Pancreatic cancer

PDAC is notoriously resistant to immunotherapy. However, recent studies have shown the potential of adjuvant vaccination strategies for the treatment of PDAC. BNT122 (autogene cevumeran; NCT04161755), a personalized mRNA neoantigen vaccine encoding up to 20 TSAs, was evaluated in a phase I trial in combination with atezolizumab and mFOLFIRINOX chemotherapy in patients with resectable PDAC. The vaccine induced long-lived, polyfunctional neoantigen-specific CD8 T cell responses in 50% of patients (8/16); these responses correlated with delayed tumor recurrence [40,98]. A global phase II trial (IMCODE003; NCT05968326) is currently ongoing to assess its clinical efficacy further. In parallel, a fixed "off-the-shelf" mRNA vaccine targeting the hotspot KRAS G12V mutation showed early signs of clinical benefit, including neoantigen-specific T cell responses and tumor shrinkage, in patients with advanced PDAC [119]. Additionally, a phase I/II trial of a DC-based vaccine, composed of autologous DCs pulsed with allogeneic mesothelioma tumor cell lysate (comprising antigens also expressed in PDAC), achieved a two-year recurrence-free survival rate of 64%, meeting its primary endpoint [207]. Notably, a patient with recurrent end-stage PDAC achieved the complete remission (CR) of primary and metastatic lesions without chemotherapy after treatment with a combination of α-GalCer–pulsed DC vaccine, WT1 DC vaccine, and NK cell therapy, highlighting the potential of multimodal immune cell–based strategies even in chemotherapy-refractory settings [208].

NSCLC

mRNA-based vaccines are emerging as a promising immunotherapeutic strategy for NSCLC, aiming to elicit antigen-specific immune responses and enhance the efficacy of existing treatments. Early-generation fixed antigen vaccines, such as CV9201 (NCT00923312) [115] and CV9202 (NCT01915524 [101,102] and NCT03164772 [103]), encoding up to six NSCLC TAAs (MAGE-C1, MAGE-C2, NY-ESO-1, Survivin, 5T4, and MUC-1), demonstrated good safety profiles and T cell immunogenicity in phase I/II trials. CV9202, in particular, induced antigen-specific responses in over 80% of patients and showed signs of disease control, with partial responses or stable disease observed in nearly half of treated patients when combined with local radiotherapy [101]. Next-generation vaccines, such as BNT116 (NCT05142189) [166], also targeting fixed TAAs, are being evaluated in combination with ICIs (e.g., cemiplimab) or chemotherapy in ongoing phase I trials for advanced or metastatic NSCLC. Though still in the early phases, this approach reflects a shift toward rational combination strategies to boost clinical efficacy. In parallel, mRNA-4157 (V940), which encodes up to 34 individualized neoantigens, is being evaluated in advanced NSCLC. Preliminary studies have demonstrated robust neoantigen-specific CD8 T cell responses and a favorable safety profile, supporting its advancement to a phase III adjuvant trial in NSCLC (NCT06077760) and highlighting its translational potential beyond melanoma [177]. In addition, mutation-targeted vaccines, like mRNA-5671 (NCT03948763), which encodes four KRAS hotspot mutations (G12C, G12D, G12V, and G13D), have shown safety and immunogenicity in early-phase studies involving KRAS mutant NSCLC and colorectal, and pancreatic cancers, although efficacy results remain limited. Collectively, these approaches illustrate the versatility of mRNA vaccine platforms, which range from fixed antigen designs to individualized therapies, and their potential when combined with ICIs or standard-of-care treatments in NSCLC.

Prostate cancer

The clinical application of mRNA-based vaccines in prostate cancer has been explored through direct mRNA vaccines and mRNA-transfected DC vaccination strategies. Early trials of direct mRNA vaccines, such as CV9103 (NCT00906243 and NCT00831467) [115] and its successor CV9104 (NCT02140138 and NCT01817738 [100]), targeted up to six prostate TAAs (PSA, PSMA, PSCA, STEAP1, prostatic acid phosphatase [PAP], and MUC1) and demonstrated favorable safety and immunogenicity. However, phase 2b data showed limited clinical efficacy, potentially confounded by the introduction of new life-prolonging therapies during the trial period. Recently, BNT112 (NCT04382898) [164], a lipoplex-formulated mRNA vaccine encoding five prostate-specific TAAs (PAP, PSA/KLK3, KLK2, HOXB13, and NKX3-1), showed encouraging immune and PSA responses in a phase 1/2 trial, particularly when combined with the PD-1 inhibitor cemiplimab. However, its long-term efficacy remains under investigation.

In parallel, personalized mRNA-transfected DC vaccines have been explored in metastatic and high-risk localized prostate cancer. For example, GRNVAC1 (AST-VAC1) is a DC-based mRNA vaccine encoding human telomerase reverse transcriptase (hTERT), a

widely expressed TAA, and lysosome-associated membrane protein-1, which directs antigen processing through the MHC class II pathway to enhance T cell activation; it has been demonstrated to induce antigen-specific CD4 and CD8 T cell responses in patients with metastatic prostate cancer [209]. Another trial (NCT01446731 [210]) evaluated DCs transfected with PSA, PAP, Survivin, and hTERT mRNA in combination with docetaxel in patients with metastatic castration-resistant prostate cancer (mCRPC), demonstrating good tolerability and safety, albeit with limited survival benefit. Additionally, a phase 1/2 study (NCT01197625) assessed personalized DC vaccines loaded with autologous tumor-derived antigens or with hTERT and Survivin mRNA as an adjuvant therapy for high-risk prostate cancer after radical prostatectomy, showing positive results [111]. Finally, Sipuleucel-T (Provenge, NCT00065442) [211], an autologous DC-based vaccine activated *ex vivo* with a prostatic acid phosphatase (PAP)–GM-CSF fusion protein, greatly prolonged the overall survival of men with mCRPC in a phase III clinical trial, becoming the first FDA-approved cancer vaccine.

GBM

mRNA vaccines have shown increasing clinical promise in the treatment of GBM, a highly lethal brain cancer. One innovative approach involves the use of multilamellar “onion-like” RNA–lipid particle aggregates (RNA–LPAs; NCT04573140) [56], which enhance mRNA antigen packaging and activate the RIG-I pathway in stromal cells, thereby mimicking viral infection and promoting robust cytokine release, DC recruitment, and TME immunogenic reprogramming. Preclinical studies in pet dogs with terminal glioma demonstrated improved survival and effectively “reprogrammed” the TME to become “hot” within days of a single RNA–LPA infusion. In a first-in-human trial (NCT04573140), RNA–LPAs induced rapid cytokine/chemokine release, immune activation/trafficking, glioma-specific T cell responses, and radiologic evidence of pseudoprogression in patients with GBM [56]. Another ongoing phase I trial (NCT06389591) is evaluating RNA–LPA vaccines comprising pp65 and personalized tumor RNA in adults with recurrent GBM.

In parallel, DC-based mRNA vaccines have demonstrated clinical efficacy. These vaccines typically target TAAs, such as CMV pp65 or WT1, and are often combined with immunomodulatory agents like temozolomide, GM-CSF, or tetanus toxoid (Td). A phase I/II trial (NCT00961844) using mRNA-transfected DCs targeting autologous glioma stem cells reported a 2.9-fold improvement in progression-free survival compared with historical controls [192]. Additionally, DC vaccines loaded with CMV pp65 mRNA, particularly when combined with lymphodepleting temozolomide and Td preconditioning, achieved durable responses, with one cohort exhibiting a median progression-free survival of 25.3 months [189]. Several trials, including NCT02366728 and NCT0369639, have demonstrated the feasibility and safety of these approaches, showing promising signs of immune activation and prolonged survival [110]. These findings support the feasibility and therapeutic potential of mRNA-based immunotherapies in GBM.

Hematological malignancies

While mRNA vaccines have shown remarkable progress in solid tumors, their application in hematological malignancies is advancing cautiously, reflecting several profound biological and clinical challenges unique to these diseases. In contrast to that in many patients with solid tumors, the immune system in patients with acute leukemias or advanced myelodysplastic syndrome (MDS) is often inherently dysfunctional, with impaired T and dendritic cell function compromising the ability to mount an effective vaccine response [38,212,213]. Furthermore, the aggressive nature of acute leukemias creates a logistical conflict with the prolonged manufacturing timelines required for personalized vaccines. The immunosuppressive bone marrow microenvironment and the tendency for leukemic blasts to downregulate MHC molecules for immune escape present additional important hurdles [214,215].

The above challenges explain why research has largely focused on strategies adapted to this unique context. For instance, DC-based vaccines loaded with shared TAAs like WT1 remain a primary approach [109,186]. Moreover, a strong rationale exists for administering vaccines during periods of low disease burden and good immune function, such as in the CR setting, to prevent or delay relapse. In parallel, research continues to identify novel immunotherapy targets, including neoantigens from mutations (indels) or mis-splicing events (e.g., SRSF2 and ZRSR2) [38] in MDS and AML, which are being explored primarily through TCR-based therapies but hold promise for future mRNA vaccine applications.

AML

In AML, mRNA-based vaccine strategies are primarily centered on DC vaccines, where autologous DCs are loaded *ex vivo* with mRNA-encoding TAAs, such as WT1, hTERT, and Survivin (NCT05000801). Phase 2 trials (NCT00834002 and NCT01686334) [186] have demonstrated that WT1 mRNA–electroporated DC vaccines are safe and may markedly reduce relapse risk and improve long-term relapse-free survival in patients with AML achieving first CR. Likewise, hTERT-

targeting DC vaccines (NCT00510133) [108] have shown feasibility in early trials. FDC101 (NCT02405338) [109], an autologous DC mRNA vaccine encoding WT1 and PRAME, demonstrated good tolerability and favorable long-term survival as a maintenance approach in patients with AML in first CR who were ineligible for allogeneic stem cell transplantation. Beyond shared TAAs, recent insights into AML-specific indel mutations provide a potential basis for developing personalized neoantigen-targeting mRNA vaccines, although these vaccines remain at the preclinical stage [216]. Among potential neoantigen sources, fusion gene–derived neoantigens have emerged as particularly promising targets. For instance, the CBFB::MYH11 fusion generates immunogenic peptides, such as REEMEVHEL, which are recognized by HLA-B*40:01-restricted TCRs. These TCRs exhibit potent antileukemic activity *in vitro* against primary AML samples and *in vivo* in patient-derived xenograft models, effectively controlling AML progression [127]. Although PML::RARA-derived peptides in acute promyelocytic leukemia (APL) can trigger CD4 T cell responses *in vitro*, further evidence is needed to confirm their natural processing and presentation on APL cells [128]. Other leukemia-associated fusion genes, including PICALM::MLLT10 and NUP98::NSD1, have also been shown to generate neoantigen-specific TCRs in AML [129]. Notably, PICALM::MLLT10-specific TCRs (e.g., SJAML030459_5) are presented by HLA-B51:01 and induce 4-1BB expression, whereas NUP98::NSD1-targeting TCRs (e.g., SJAML001441_2) demonstrate cytotoxicity against leukemia cells *in vitro* [129]. However, the overall efficacy of mRNA vaccines in AML may be constrained by immune dysfunction in patients with active or progressive disease, highlighting the need for combination strategies or postremission interventions in these patient populations.

MDS

mRNA vaccine research on MDS remains in the early stage but conceptually overlaps with that on AML. Neoepitopes arising from splicing factor mutations (SRSF2 and ZRSR2) have been identified as potential immunotherapy targets. Although current studies focus primarily on TCR-based therapies, they pave the way for future mRNA applications [38]. WT1-based vaccination (NCT03083054) has also been explored in patients with MDS.

Lymphoma

mRNA vaccine strategies for lymphoma, particularly EBV-driven subtypes, has seen broadened exploration. The WGc-043 mRNA vaccine, currently in a phase I trial, specifically targets EBV-associated oncogenic pathways in NK/T cell lymphoma [217]. In parallel, the intravenous delivery of mRNA vaccines is being evaluated in a phase I study (NCT05714748) for EBV-related refractory malignancies, including lymphomas. mRNA-encoded immunomodulators, such as OX40L, IL-23, and IL-36γ (mRNA-2752; NCT03739931) [218,219] are being tested to boost antitumor immunity in lymphomas and solid tumors beyond targeting viral antigens. Additionally, in B cell non-Hodgkin's lymphoma, bbT369, an mRNA-modified CAR-T cell therapy, is under phase 1/2 investigation (NCT05169489) [220] as a dual-targeting strategy for relapsed or refractory disease.

Multiple myeloma and chronic lymphocytic leukemia

Although clinical trials of mRNA vaccines in multiple myeloma (MM) are limited, a phase 1 study (NCT01995708) [203] demonstrated that postautologous stem cell transplantation vaccination with autologous DCs electroporated with mRNAs encoding CT7, MAGE-A3, and WT1 is safe and elicits robust tumor-specific immune responses, supporting the feasibility of mRNA-based immunotherapy in the posttransplant setting. Recent innovations include an mRNA vaccine targeting BCMA in MM, encapsulating optimized BCMA mRNA with or without a TLR3 agonist (poly(I:C)) in LNPs. Preclinical models showed that DC uptake led to potent BCMA-specific CD8 T cell activation and tumor inhibition [133]. In addition to mRNA vaccines, *in vivo* CAR-T strategies are progressing. ESO-T01 uses a nanobody-targeted lentiviral vector for the reprogramming of endogenous T cells, bypassing *ex vivo* manufacturing. In a first-in-human phase 1 study (NCT06691685), four patients with relapsed/refractory MM received a single ESO-T01 infusion, resulting in manageable side effects and detectable functional CAR-T cells, along with early signs of antitumor activity, including the eradication of extramedullary disease [221].

In CLL, mRNA vaccine development remains conceptual, without ongoing clinical trials. Existing efforts have primarily centered on personalized peptide vaccines, such as the iVAC-CLL-XS15 trial (NCT04688385) [222] in CLL and the OpenVax platform (NCT02721043) [223] including patients with MM. Nonetheless, extensive neoantigen profiling in both diseases has yielded key insights, offering a valuable foundation for future mRNA vaccine design.

Safety profile of mRNA-based cancer immunotherapies

mRNA-based therapies have generally demonstrated a favorable safety and tolerability profile in numerous clinical trials. While extensive clinical experience with

infectious disease vaccines provides a broad foundation for their safety, the specific context of cancer immunotherapy presents a unique set of considerations.

For intravenously delivered mRNA vaccines, such as RNA–LNP/RNA–LPX formulations, adverse events (AEs) are predominantly systemic rather than local. Injection site reactions are generally mild and infrequent and are rarely reported as major safety concerns. The most common AEs are transient, mild-to-moderate (grade 1–2) flu-like symptoms, such as pyrexia, chills, headache, fatigue, and nausea [39,40,98]. These symptoms largely reflect the rapid systemic activation of innate immunity. For instance, in the phase I trial of BNT111 for advanced melanoma, the vaccine induced a dose-dependent and pulsatile release of plasma cytokines, including IFN-α and IL-6. This cytokine secretion was transient, peaking a few hours after injection and normalizing within 24 h; this effect is directly correlated with the observed clinical profile of self-limiting, flu-like symptoms, such as pyrexia and chills [54]. However, when mRNA vaccines are used in complex combination regimens, the risk of immune-related AEs can be amplified. A key example is the phase 1/2 BNT211 trial, which evaluated CLDN6-targeted CAR-T cells combined with an mRNA vaccine booster (CARVac) in patients with relapsed/refractory solid tumors. In this setting, the toxicity profile was manageable but highly pronounced: cytokine release syndrome was observed in 46% of patients (10/22), including one patient who experienced a grade 3 event and one patient who experienced grade 1 immune effector cell–associated neurotoxicity syndrome. Dose-limiting toxicities occurred in two patients at an increased dose level but were fully resolved [57].

By contrast, similar to that observed with naked mRNA or DC-based vaccines, the safety profile of locally administered mRNA (e.g., intradermal or intranodal) is dominated by local reactions and shows a remarkably reduced risk of systemic toxicity. The most common AEs are injection site reactions, including pain, erythema, swelling, and induration [101,108]. For example, trials of the CV9202 vaccine in patients with NSCLC reported that injection site reactions and flu-like symptoms were the most common treatment-related AE [101]. These local inflammatory reactions are often considered beneficial because they help recruit immune cells to the site of vaccination. The safety profile is further improved with DC-based vaccines [206,207]. A compelling example is the LK101 trial, a neoantigen-based mRNA-loaded DC vaccine. In this study, all reported AEs were grades 1–2. The most frequent AEs were injection site reactions, including local pain (63.6%) and itching (27.3%) [206]. The complete absence of grade 3 or higher toxicities underscores the minimal systemic risk of this approach. Such negligible risk is attributed to the mRNA being contained within DCs, thus preventing a widespread, uncontrolled innate immune response.

Collectively, these findings underscore that while mRNA cancer vaccines are largely well tolerated, particularly as monotherapy, careful dose optimization and vigilant immune monitoring are essential when they are integrated into complex, multimodal treatment paradigms, like combination with cell therapies.

Challenges and limitations

Despite their considerable promise, the translation of mRNA vaccines into broadly effective cancer therapies requires overcoming several formidable hurdles related to tumor biology, drug delivery, and manufacturing.

First, the immunosuppressive TME remains a primary barrier [18,224,225]. The dense infiltration of regulatory T cells [226], myeloid-derived suppressor cells [227,228], tumor-associated macrophages [229,230], tumor-associated neutrophils, cancer-associated fibroblasts [231,232], immunosuppressive cytokines (e.g., TGF-β and IL-10) [233–235], and immune checkpoints (e.g., PD-L1) [236] actively dampen vaccine-induced immune responses. This situation limits the efficacy of mRNA monotherapy and supports the rational design of combination strategies. While pairing with ICIs is the most established strategy, future approaches may involve codelivering mRNA encoding for immunomodulatory molecules (e.g., cytokines) or combining vaccines with agents that target specific suppressive cell populations.

Second, the effective delivery of mRNA therapeutics, particularly to solid tumors, remains a central challenge that involves tumor-specific physical barriers and systemic physiologic constraints. Within solid tumors, the dense extracellular matrix (ECM), which is rich in collagen and hyaluronan, forms a physical sieve that, together with elevated interstitial fluid pressure, restricts the penetration of LNPs beyond the perivascular space [237]. The aberrant and tortuous tumor vasculature further contributes to heterogeneous perfusion, resulting in the uneven distribution of the mRNA vaccine. Systemically, intravenously administered LNPs are rapidly opsonized by plasma proteins, marking them for clearance by the reticuloendothelial system, primarily macrophages in the liver and spleen. This process leads to substantial off-target accumulation, diminished delivery efficiency to tumor sites, and potential hepatotoxicity [41,238]. In addition, the immunogenicity of certain delivery vehicles may elicit antidrug antibody responses, compromising the efficacy of repeated dosing [18,19]. Several innovative strategies have been proposed to overcome these formidable challenges. Active targeting approaches functionalize LNP surfaces with ligands (e.g., antibodies and aptamers) that recognize receptors overexpressed on tumor or immune cells, such as T cells [138,239]. TME remodeling strategies, including the

coadministration of ECM-degrading enzymes, like hyaluronidase [240], represent a promising approach to enhance nanoparticle penetration. Furthermore, stimulus-responsive "smart" systems, designed to release their mRNA cargo in response to tumor-specific cues, such as acidic pH or elevated enzymatic activity, represent a rapidly advancing frontier [133,241]. Collectively, these next-generation platforms offer promising avenues to enhance the specificity, safety, and therapeutic efficacy of mRNA-based cancer immunotherapies.

Third, in hematologic malignancies, challenges are compounded by profound host immune dysfunction and rapid disease progression. This situation is particularly evident in AML, which is generally considered an immunologically cold tumor [214] characterized by low MHC-I expression [215], limited T cell infiltration, and functional T cell impairment [38,212]. The inherent impairment of the hematopoietic system limits the patient's ability to mount a robust immune response. Personalized neoantigen vaccines face additional limitations because of prolonged manufacturing timelines, particularly for complex and large-scale DC vaccine productions that may take one month to three months, often conflicting with the urgent treatment demands of aggressive diseases, such as AML [13]. Emerging solutions here focus on alternative therapeutic windows and targets. These solutions include using vaccines as a maintenance therapy in the postremission setting to prevent relapse and developing "off-the-shelf" vaccines targeting shared antigens like fusion gene products.

Finally, on the manufacturing front, scaling up high-quality mRNA production remains challenging. Key issues include efficient capping; removal of immunogenic byproducts, such as dsRNA; and maintaining rigorous quality control [23,112,113]. The emerging solution involves innovations in production platforms, including improved enzymatic reactions and advanced purification techniques, like chromatography, which aim to streamline and standardize manufacturing.

Together, these immunological, physical, systemic, and manufacturing challenges highlight the need for continued innovation in delivery technologies, combination strategies, and production platforms to fully unlock the therapeutic potential of mRNA vaccines in cancer.

Perspectives

mRNA technology has rapidly evolved from a scientific curiosity to a transformative therapeutic platform, driven by advances in molecular design, delivery systems, and scalable manufacturing. Its unprecedented success during the COVID-19 pandemic validated the broad potential of mRNA therapeutics across diverse diseases, providing a blueprint for rapid clinical translation. This progress reflects not a single scientific breakthrough but the synergistic integration of multiple disciplines, including molecular biology (mRNA sequence engineering), materials science (delivery systems like LNPs), chemical engineering (manufacturing optimization), and immunology/oncology (mechanistic understanding and clinical applications), underscoring the critical need for continued interdisciplinary collaboration to sustain future innovation. In oncology, the synergy of personalized mRNA vaccines with ICIs in challenging malignancies, such as melanoma and pancreatic adenocarcinoma, represents a landmark achievement [40,55,98,123]. However, the future trajectory of mRNA-based cancer immunotherapy will be defined by strategic advancements in several key areas, moving beyond current paradigms to address existing hurdles and unlock the platform's full potential.

Expanding the antigenic repertoire: toward nonclassical vaccines

While personalized neoantigen vaccines exemplify precision medicine, the field is increasingly exploring novel, broadly applicable antigenic sources to create applicable, "off-the-shelf" therapies. Beyond classical mutation-derived neoantigens, research on mRNA cancer vaccines is increasingly exploring novel antigenic sources with broad therapeutic potential. Key emerging targets include noncanonical ORF–derived peptides, often translated from unannotated regions, such as UTRs, lncRNAs, or internal ORFs. These cryptic, aberrantly expressed TSAs (aeTSAs) are frequently tumor-restricted and, in many cases, shared across patients, as demonstrated in PDAC [37] and B-ALL [242]. Similarly, recurrent splice-site mutations in factors, such as SRSF2 and ZRSR2 (common in AML and MDS), give rise to highly immunogenic, stereotyped neoepitopes that serve as public targets for TCR-based therapies [38]. Transposable element–derived antigens, particularly from endogenous retroviral elements, offer another class of nonmutated, shared, and highly immunogenic aeTSAs [22]. Together, these nontraditional antigen sources broaden the mRNA vaccine landscape, enabling novel immunotherapeutic strategies that target tumor-specific but mutation-independent antigens. Importantly, *de novo* designed TCR mimics or minibinders specific for pMHCs offer a promising avenue to unlock this hidden antigenic repertoire, enabling highly selective and personalized immunotherapies with extended applicability [143–145].

Next-generation delivery systems: achieving precision and control

Future progress is inextricably linked to innovations in

delivery. The field is actively moving beyond conventional LNPs toward next-generation, highly targeted delivery systems. Such systems include ligand-modified and hybrid nanoparticles engineered for precise delivery to specific cell types and tissues [138,239]. Another major frontier is the development of "smart" stimulus-responsive nanoparticles that release their mRNA payload only in response to the unique conditions of the tumor microenvironment (e.g., low pH) [133,241]. These advanced platforms promise to enhance the therapeutic index considerably by maximizing efficacy while minimizing the systemic administration challenges of degradation and off-target accumulation.

Rise of AI-driven, end-to-end vaccine design

Advancements in mRNA design will be increasingly driven by AI and ML. The future lies in an integrated, "end-to-end" computational pipeline that can rationally design a vaccine with unprecedented speed and precision [92]. This workflow will encompass the AI-powered prediction of the most immunogenic neoantigens from multiomics data, deep learning–based optimization of mRNA stability and translation efficiency, and data-driven prediction of optimal LNP formulations [89–91]. By analyzing vast data sets, these technologies will not only enhance efficacy but also improve scalability and ultimately reduce the cost of these transformative therapies.

Sophisticated combination therapies and expanded applications

The future of mRNA in oncology will be defined by its role as a cornerstone of complex combination therapies. While synergy with ICIs is established, the platform's ability to prime and activate a targeted immune response makes it an ideal partner for other modalities, such as cell therapies (e.g., mRNA vaccines to boost CAR-T cell persistence), and other agents that overcome resistance mechanisms [57,131,138]. Looking even further ahead, the scope of mRNA therapeutics is rapidly expanding beyond vaccines to encompass protein replacement therapies, treatments for genetic disorders, and *in vivo* cell engineering, all of which will benefit from the ongoing innovations in this dynamic field.

In conclusion, the versatility and rapid adaptability of mRNA technology position it to revolutionize precision medicine. This field, which is characterized by relentless innovation and deep interdisciplinary collaboration encompassing molecular biology and materials science to immunology and data science, is steadily advancing toward a future of safe, effective, and increasingly personalized therapeutic solutions for a wide range of diseases.

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Compliance with ethics guidelines

Conflicts of interest Niu Qiao, Jing-Xian Chen, Yan Liu, and Zhu Chen declare no competing interests. Sai-Juan Chen is the Editor-in-Chief of *MedScience* and was excluded from peer review and all editorial decisions related to the acceptance and publication of this article. Peer review was handled independently by other editors to minimize bias.

This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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