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REVIEW ARTICLE

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mRNA cancer vaccines: A new paradigm for personalized immunotherapy

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ABSTRACT

Background: With messenger RNA (mRNA) vaccines, cancer immunotherapy is changing to an entirely different ballpark. These vaccines enable rapid prototyping and simultaneous antigen presentation to stimulate strong responses from both CD8+ and CD4+ T cells. This review aims to integrate the current developments and the future direction of this developing technology.

Key Advances: Constructing an effective vaccine clinically useful was made possible by the sequential advancements in technology, such as nucleoside modifications (e.g., pseudouridine) to enhance stability and translation, codon and untranslated region sequence optimization, and lipid nanoparticle (LNP) delivery systems to ensure *in vivo* uptake. Such advancements make constructing off-the-shelf and bespoke neoantigen vaccines possible.

Clinical Impact: Personalized mRNA vaccines have been effective when combined with immune checkpoint inhibitors. In the case of resected melanoma, the combination of mRNA-4157 and pembrolizumab reduced the risk of recurrence by 44% hazard ratio (HR = 0.56). BNT122's recurrence-free survival at 18 months was 79%. There is a similar indication of efficacy for pancreatic cancers and microsatellite-stable colorectal cancers.

Challenges and Future Directions: Persisting issues include the variability of tumors, immunosuppressive microenvironments, inefficiency of LNP (such as hepatic sequestration), and complicated, high-cost manufacturing (>$100,000/dose). Artificial Intelligence antigen prediction, next-generation delivery platforms for targeted lymphoid tissue accumulation, and combination strategies with stromal modulators will be critical to address in the future. To enhance global access, innovations in manufacturing at scale and prophylactic vaccination for high-risk populations are required.

Conclusion: Taking into account the regulatory approvals and the ongoing Phase-III trials, it seems that mRNA vaccines will soon lead to a breakthrough in personalized oncology, shifting the paradigm of treatment from immediate intervention to chronic care and prevention.

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Introduction

With an estimated death toll of 10 million people in 2020, cancer remains a public health threat worldwide [1]. In the past, the treatment of cancer relied on surgery, chemotherapy, and radiation therapy, all of which had a high likelihood of failure and recurrence of cancer. The metastatic diseases face most of such therapies [2]. The development of cancer immunotherapy, especially immune checkpoint inhibitors (ICIs) focusing on PD-1 and CTLA-4 pathways, paved the way for cancer treatment, and the host immune system was further enabled to bring long-lasting and, in some cases, curative responses [3]. The majority of patients still face primary or acquired resistance to ICIs, posing a significant humanitarian problem and a strong call for developing therapies to target the more effective priming and activation of anti-tumor immunity [4,5]. Therapeutic Cancer Vaccines represent a promising strategy to overcome immune tolerance

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by generating T-cell responses against tumor-associated antigens (TAAs) or tumor-specific neoantigens. Vaccine strategies using peptides, proteins, dendritic cells (DCs), or viral vectors have, in the past, shown scant clinical benefits [6–8]. These vaccines from the past era have more than one reason for their failure. Among other reasons, they have extremely low immunogenicity and immune tolerance against self-antigens to offer. Their methods of antigen presentation are not very effective, and on top of their antigens being susceptible to attack by the tumor microenvironment, there is simply not enough generation of cytotoxic CD8+ T cells (CTLs) [9].

The SARS-CoV-2 pandemic, along with messenger RNA (mRNA) vaccines recent success has put such technology at the forefront of modern science [10,11]. Despite this, the core focus for such technology has always been oncology. Given the progress in the last 20 years, such mRNA-based therapies would not face the initial challenges of fragile stability and strong immunogenicity. Important innovations include nucleoside modifications (e.g., pseudouridine) to dampen innate immune recognition and improve translation capacity [12,13], advanced sequence tuning of untranslated regions (UTRs), codon optimization, and capping structures to boost protein output [14], as well as lipid nanoparticle (LNP) technology to ermöglichen biologically relevant delivery and endosomal escape [15,16]. Vaccines based on mRNA, as opposed to other methods, bring an impressive list of benefits. Her personalized neoantigen vaccines, which are shaped based on specific mutations, rely on their creation, mRNA's speed and adaptability are crucial. There are no chances of mRNA integrating into the genome, in contrast to viral vectors, and mRNA can be administered multiple times since there is no previous anti-vector immunity [17]. The mRNA gets translated within the cell, allowing the antigen to be processed and presented naturally. It can be displayed on both major histocompatibility complex (MHC) class I and II molecules, thus supporting the activation of CD8+ and CD4+ T-cell responses at the same time. This is vital for the initiation and maintenance of strong anti-tumor immunity [18,19].

While the potential of mRNA cancer vaccines is immense, a number of issues remain concerning their clinical application. These include the accurate selection of immunogenic neoantigens from the tumor's heterogeneous mass, mRNA's delivery to the therapeutically relevant tissues, the need to bypass a deeply immunosuppressive tumour microenvironment, and the challenging economic and logistic issues of producing personalised therapeutics at a clinical scale [20,21].

This review aims to highlight the issues of mRNA cancer vaccines of today and the possible issues of tomorrow, taking into account the role these vaccines can play in shifting mRNA therapies in a new direction of cancer immunotherapy. We will explain the mechanistic principles behind the elicitation of anti-cancer immune responses, describe the sophisticated design and formulation strategies behind their efficacy, and describe the different vaccine types in development. The existing modern clinical trials will be deeply evaluated, extracting efficacy and safety signals. Additionally, we will directly address the existing biological, technological, and financial barriers. Lastly, we will discuss the emerging paradigm shifts, including Artificial Intelligence-based antigen discovery, next-generation delivery platforms, combination therapies, and the provocative possibility of vaccination in prophylactic settings for high-risk populations. By integrating these components, this work intends to illustrate the distinctive role of mRNA vaccines for the previously unreachable personal oncology, shifting from the battle with the acute illness to the area of sustained control and prevention.

Mechanism of Action: How mRNA Vaccines Elicit Anti-Tumor Immunity

Core principles of mRNA vaccine immunology

An mRNA cancer vaccine is designed to introduce *in vitro*-transcribed (IVT) mRNA sequences of tumor antigens directly into the patient's cells, hence leveraging the cellular mechanisms to produce the desired proteins and triggering strong and targeted adaptive immunity [10,17]. The classical antigen vaccines work by delivering already-made proteins or their peptide fragments, whereas mRNA vaccines act as temporary genetic instructions. This makes them fundamentally different, as they can simulate a viral infection while allowing internal production, processing, and presentation of antigens through the MHC class I and II pathways. Such simultaneous presentation is necessary to orchestrate the synergy between cytotoxic T cells, CTLs, and CD4+ T-helper cells, the foundation of robust anti-cancer immune responses [18,19]. In this context, DCs are regarded as the most important antigen-presenting cells (APCs) and act as "natural adjuvants" because of their superior ability to take up, process, and present antigens and their ability to travel to lymph

nodes and activate naïve T cells [22]. The functions of LNPs are vital to this process. They help keep the mRNA intact while enabling its delivery to the cytosol of APCs via endosomal escape [15,16].

Step-by-step immunological cascade

The induction of immunity by mRNA-LNP vaccines is a coordinated multi-step process (Fig. 1).

Cellular uptake and endosomal escape: After intramuscular or subcutaneous administration, mRNA-LNPs are mainly taken up by local APCs, such as dendritic cells and macrophages, through endocytic mechanisms [15]. The ionizable lipids of the LNPs undergo structural changes that cause fusion with the endosomal membrane and the release of the mRNA cargo into the cytosol. This process is triggered by a drop in pH within the endosome, which is a rate-limiting step for efficacy [17].

Antigen translation and processing: Tumor antigens encoded by released mRNA undergo translation by ribosomes. The preceding steps of immune activation rely fully on the outcome of that protein. The proteasome degrades cytosolic antigens into short peptides, which are then shuttled to the endoplasmic reticulum by the transporter associated with antigen processing, where they are loaded onto MHC class I molecules and presented to CD8+ T cells. In one alternative scenario, antigens that are secreted or membrane-bound can be processed by APCs through endocytosis, and in endolysosomal compartments, they are processed and loaded onto MHC class II molecules to be recognized by CD4+ T cells [18,23].

DC maturation and migration: Among the notable features of mRNA is its ability to stimulate

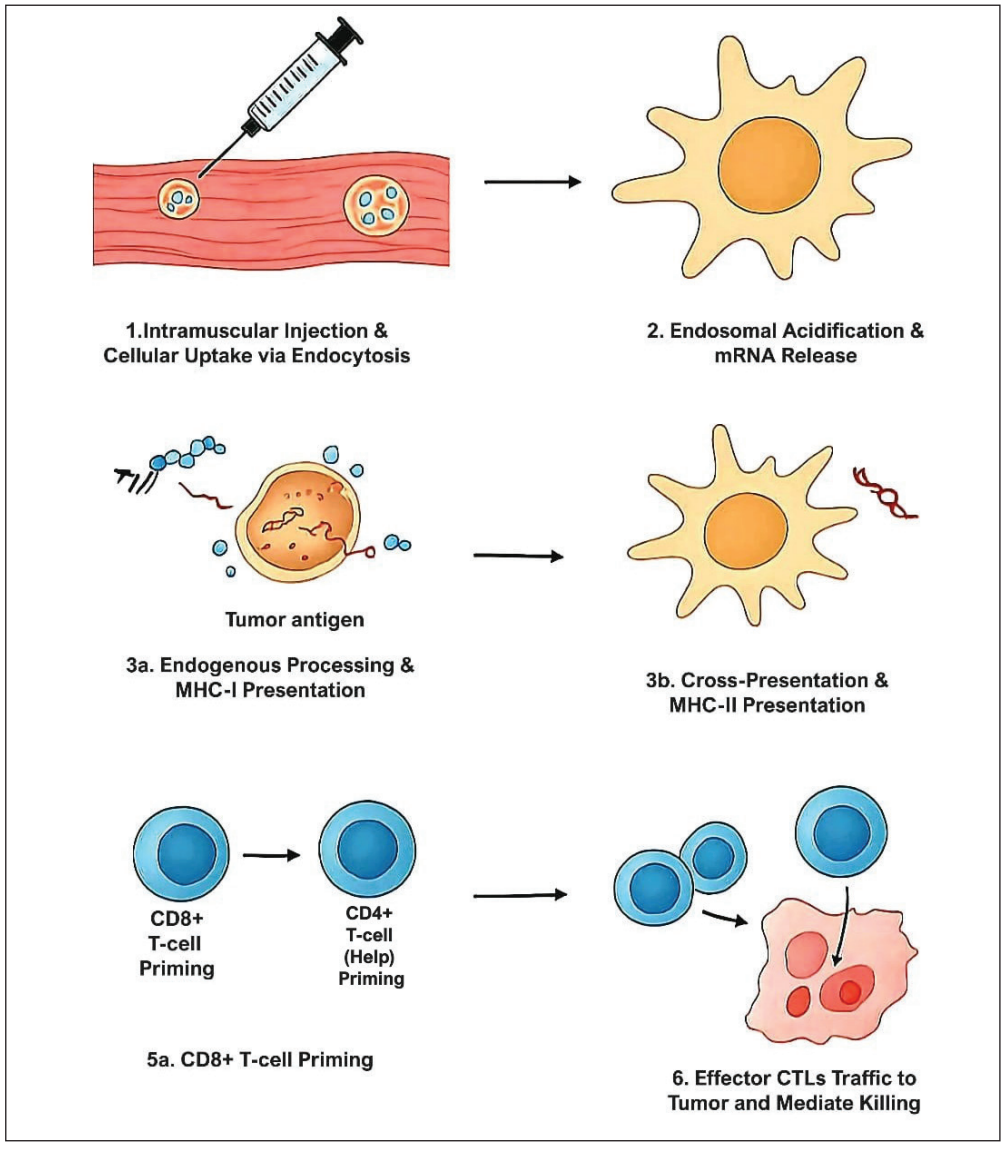

Figure 1. Mechanism of action of mRNA-LNP cancer vaccines.

an immune response. External mRNA is sensed by endosomal Toll-like receptors (e.g., TLR7/8) and cytosolic receptors such as Retinoic acid-Inducible Gene I (RIG-I), which leads to the strong production of type I interferon and the initiation of DCs maturation [12,24]. The emergence of maturation is marked by the increased expression of co-stimulatory molecules (CD80, CD86, and CD40) and the chemokine receptor CCR7, which guides the mature, antigen-loaded DCs to the draining lymph node [25].

T-Cell priming and differentiation: In the lymph node, mature dendritic cells present a complex between a peptide derived from an antigen and an MHC molecule to naive T lymphocytes. The engagement of T-cell receptors (TCRs) provides the first signal. Co-stimulatory signals provide the second, and cytokine signals (for example, IL-12) provide the third. The three together provide for cytokine activation and differentiation of T cells.

- CD8+ T cells that identify peptide-MHC-I complexes evolve into CTLs that can destroy tumor cells.
- CD4+ T cells that recognize peptide-MHC-II complexes turn into T-helper 1 cells, which release IFN-γ and lead to critical support for the maintenance and enhancement of CTL responses [26].

Tumor infiltration and killing: The vaccine-primed CTLs initially leave the lymph nodes and start the circulation, after which they infiltrate the tumor beds. They continue tumor surveillance, identify their relevant antigens presented on MHC-I of tumor cells, and continue with cytotoxic functions. These cytotoxic activities include the targeted release of perforin and granzymes, death receptors (e.g., FAS-FASL) engagement, and secretion of cytokines such as IFN-γ. Cytokines not only inhibit angiogenesis but also activate other immune cells, such as macrophages [27]. The endpoint of a successful immune response is the formation of long-lived memory T cells, which may include the effector memory (T_EM) and central memory (T_CM) subsets. These cells take care of immunosurveillance and enable quick recall responses once the antigen is detected again, hence ensuring long-term disease control [18].

Comparative analysis with alternative vaccine platforms

Because of their mRNA structure, these vaccines present their own advantages and restrictions, which differ from those of other vaccines (Table 1). One of the important advantages mRNA vaccines present is the ability to present antigens endogenously on class I and class II histocompatibility molecules on mRNA, therefore inducing strong and multifunctional CD8+ and CD4+ T cell responses. This feature is usually not present in peptide vaccines [18]. Compared to viral vector mRNA vaccines, they do not have the danger of integration into the genome, and they do not have vector immunity, so they can be given repeatedly and still maintain efficacy [17]. Even more importantly, personalization is possible with mRNA vaccines as they can be manufactured within weeks [23], offering their unmatched speed and flexibility in manufacturing.

The first-generation LNPs are known to exhibit liver targeting and to sequester a dose fraction [17], but coupled with the transient expression of antigen expression (from non-replicating mRNA and lasting 24–72 hours), they comprise the core limitations [15]. Together, they can result in the need to optimize prime-boost regimens. Efforts are under development on a constant basis to leverage current delivery systems to overcome this hurdle.

Design and Formulation: Engineering Effective mRNA Vaccines

Advanced bioengineering techniques to solve the problems of stability, translation, and delivery

Table 1. Comparison of various cancer caccine platforms and the delivery methods used for each platform.

Platform	Delivery method	Key advantages	Key limitations
mRNA/LNP	Nanoparticle	Rapid design/production; endogenous antigen presentation; strong CD8+/CD4+ response; no genome integration	Cold chain; LNP hepatotropism; reactogenicity
DNA Plasmid	Electroporation/viral	Room-temperature stable; long expression	Low immunogenicity; requires nuclear entry; anti-vector immunity
Peptide	Subcutaneous + adjuvant	Simple manufacturing; precise epitope targeting	HLA restriction; weak CD8+ induction; needs strong adjuvants
Viral Vector	Recombinant virus	High transduction; inherent adjuvanticity	Pre-existing immunity; insertional mutagenesis risk; complex production

have made it possible to develop mRNA vaccines. The development of an mRNA vaccine depends on multiple optimizations—the nucleotide sequence, the delivery vehicle, and the final formulation for storage.

mRNA sequence optimization

Natural mRNA degrades quickly and also, and it triggers a strong immune response. This called for the need to develop optimized IVT mRNA. This optimization requires several important changes that collectively help to improve stability, decrease innate immune response, and optimize protein expression (Fig. 2).

- **Nucleoside modifications:** The groundbreaking discovery was recognizing that the incorporation of modified nucleosides, including pseudouridine mnemonics (Ψ) or 1-methylpseudouridine (m1Ψ), into mRNA sequences significantly decreases the recognition of these sequences by TLRs. This decrease is beneficial because it weakens the unwanted type I interferon responses that can inhibit translation [12,13]. At the same time, this modification increases translational capacity by more than 100-fold. In the same way, the 5-methylcytidine modification can suppress RIG-I activation and enhance mRNA stability [28]. As far as these modifications go, a major point of concern is that too much modification can cause harm; therefore, a fine, antigen-dependent tuning is needed.
- **5' Cap structure:** The synthetic Cap 1 structure (m7GpppNmN) is critically important for the following: efficient ribosomal binding, the initiation of translation, and protection against 5' exonuclease-mediated decay. Co-transcriptional capping with efficiencies greater than 95% is now possible with advanced capping technologies, such as CleanCap® analogues. This represents a remarkable improvement over previous enzymatic approaches [29].
- **Untranslated regions:** The flanking UTR regions on the mRNA are pivotal in controlling its stability, transport, and efficiency of translation. The 5' UTR is deliberately kept short and simple, often integrating Kozak consensus sequences (GCCRCCAUGG) or sequences from highly expressed viral genes to support ribosomal scanning and proper initiation [30]. For the 3' UTR, careful modifications involve eliminating AU-rich segments that would otherwise lead to deadenylation and decay. In addition, elements that confer stability from genes such as α- or β-globin are incorporated to prolong the mRNA half-life inside the cell [31].
- **Poly(A) tail:** A rigidly defined poly(A) tail (usually about 100–150 adenosine bases) works together with the 5' cap to prevent mRNA from being broken down and to promote its translation. The length is quite important because tails that are too short or too long lead to reduced protein production [32].
- **Codon optimization:** Swapping out uncommon codons for common synonyms that match a well-stocked tRNA library in the target cell type will speed up translation and increase antigen yields.

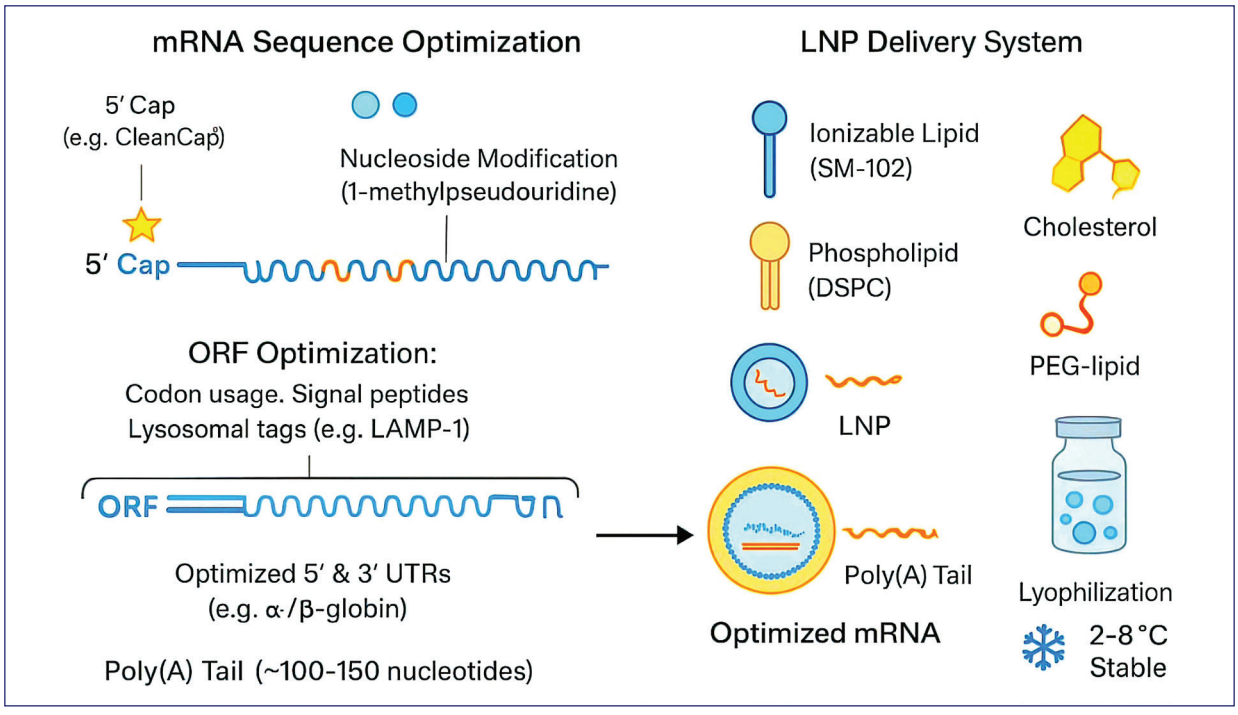

Figure 2. Engineering an effective mRNA cancer vaccine.

This tweak also tweaks the GC content to about 50%–60% so the mRNA doesn't fold into shapes that make it hard for the ribosome to keep going [33].

- **Open reading frame (ORF) design:** A well-thought-out encoded antigen can elicit very specific responses. Adding N-terminal signal peptides not only enhances secretion but also improves cross-presentation by APCs. Additionally, fusion constructs that attach the antigen to constructs such as lysosomal-associated membrane protein 1 (LAMP-1) can enhance MHC class II presentation and increase CD4+ T-cell help [34] (Table 3).

Delivery systems

There are plenty of struggles to get mRNA delivered *in vivo* effectively. It is known that mRNA without any sort of categorization is quickly broken down by extracellular RNases. Moreover, mRNA molecules are anionic, thus hindering the possibility of passive transport across the cellular membrane. Leading the struggle, lipid nanoparticles (LNPs) contain a blend of four essential components, and in relation to the struggle, all of them have remarkably distinct functions (Table 2).

The pronounced hepatotropism associated with conventional LNPs results in less than 5% of the dose reaching critical lymphoid organs. Hepatotropism results from bloodstream apolipoprotein, specifically apolipoprotein E (ApoE), which is largely responsible for LNP adsorption. This in turn results in particle transport to low-density lipoprotein receptors on hepatocytes [35]. Some mitigation strategies include lowering polyethylene glycol (PEG) content, adding cationic helper lipids (e.g., DOTAP) in Selective Organ Targeting (SORT) formulations that aim to retarget LNPs to the spleen and lymph nodes, as well as LNP functionalization with targeting ligands such as antibodies against dendritic cell surface markers like DEC-205 [18,36].

Other classes of delivery systems that are different from LNPs are polymer-lipid hybrids. One class of polymers is cationic polymers, such as polyethylenimine, and the other class is cationic nanoemulsions. Another class that is actively explored is exosomes engineered to express certain antigens. Stability, targeting, as well as ease of manufacturing are some of the advantages raised by each of these different platforms [37].

Stability and storage

The fragility of mRNA clearly requires that special care be taken in handling and formulation to maintain the effectiveness of the product all the way from manufacturing to administration. The biggest threats to it are hydrolysis from RNases and oxidative damage.

mRNA-LNP formulations are given buffers of slightly acidic compositions, such as citrate or Tris-EDTA buffer (pH ~6.5–7.0), to preserve the pKa of ionizable lipids and ensure stability during storage [38]. Freeze-drying in the presence of cryoprotectants like sucrose and trehalose profoundly benefits long-term storage because it allows vaccines to be stored at normal refrigeration temperatures (2°C–8°C) for much longer, thereby easing the strict cold chain demands of liquid formulations [39]. The wide usage of freeze-dried COVID-19 mRNA vaccines confirms that this approach can help in making vaccines more accessible worldwide.

Types of mRNA cancer vaccines

Different mRNA vaccine types have been developed using the mRNA platform's flexibility. The purpose of each vaccine type is to meet specific immune and clinical needs. These vaccine types can be mainly classified based on their structure and the origin of their antigenic targets.

Conventional non-replicating mRNA

Traditional mRNA vaccines are defined by a single ORF surrounded by optimized regulatory elements such as the 5' and 3' untranslated regions, a 5' cap, and a poly-A tail. Once it enters the cytoplasm, the mRNA is translated directly into the target antigen without any further amplification, thus enabling transient protein expression at high levels for typically 24–72 hours [17].

With billions of doses administered worldwide to combat COVID-19, this technology's most significant strength is undoubtedly its proven safety. The technology's simplicity also permits rapid and wide-scale production. This method has also shown clinical potential. For example, BioNTech's BNT111, which contains mRNAs encoding four melanoma-associated antigens (NY-ESO-1, MAGE-A3, tyrosinase, and TPTE), obtained an objective response rate (ORR) of 38.6% in advanced melanoma patients when used in combination with an anti-PD-1 antibody [40]. In a similar fashion, the CV9202 vaccine developed by CureVac targets multiple tumor-associated antigens and is intended for non-small cell lung cancer (NSCLC). This vaccine has shown a capacity to induce antigen-specific T-cell responses, which are linked to better overall survival outcomes [41]. An important drawback of this platform is the comparatively large dosage (generally 50–500 μg) needed to stimulate a strong immune response,

Table 2. Core components of lipid nanoparticles (LNPs) for mRNA delivery.

Component	Primary function	Examples
Ionizable Lipids	Neutral at physiological pH; cationic in acidic endosomes, enabling mRNA complexation and endosomal escape	SM-102, ALC-0315, DLin-MC3-DMA
Phospholipid	Provides structural integrity to the particle	DSPC
Cholesterol	Enhances membrane stability and fluidity, facilitates LNP fusion	–
PEGylated Lipid	Modulates particle size, improves colloidal stability, and reduces macrophage clearance.	ALC-0159, DMG-PEG 2000

Table 3. Key mRNA modifications and their clinical applications.

Modification	Primary function	Clinical example
Pseudouridine (Ψ)	Reduces TLR activation; enhances translation	BNT111 (BioNTech) [12]
CleanCap®	Enables >95% efficient Cap 1 incorporation	mRNA-4157 (Moderna) [29]
Optimized β-globin 3' UTR	Increases mRNA stability and translational half-life	CV8102 (CureVac) [31]

which can increase production costs and the likelihood of reactogenicity.

Self-amplifying mRNA (saRNA)

Vaccines using self-amplifying mRNA are constructed from the genome of positive-sense single-stranded RNA viruses (such as alphaviruses). Along with the antigen of interest, these vaccines include the viral replicase complex, which consists of the non-structural proteins nsP1-4. After delivery, the complex can replicate the RNA strand in the cytoplasm, which results in a significant increase in the original mRNA dose and a continuous antigen expression for weeks [42].

This self-amplification is beneficial because saRNA needs a less effective dose, which ranges between 1 and 10 μg, as compared to the conventional mRNA dose (i.e., 1/10th to 1/50th of the mRNA dose). Such a lower dose reduces cost and improves the safety profile. On the other hand, the size of saRNA constructs is much greater, ranging between 9 and 12 kb, which makes their efficient packaging into delivery vehicles a challenge. Additionally, the double-stranded RNA intermediates made in the process are strong activators of type I interferon, adjuvants that also inhibit translation and increase reactogenicity during the process. [43] Even with the challenges, advancements continue. The LUNAR-COV19 vaccine (Arcturus/CSL) proved that saRNA technology works in the clinic during the COVID-19 pandemic. In cancer, institutions like Imperial College London lead Phase I studies of saRNA-based neoantigen vaccines (e.g., NCT05929923) to study the possibility of lasting immunity.

Personalized neoantigen vaccines

Rather than focusing on universal antigens, this method marks the most advanced cancer immunotherapy by focusing on the individual patient's mutational signature (mutanome). The central idea here is that neoantigens—which emerge from somatic mutations—represent a foreign entity for the immune system and, as a result, are not influenced by central tolerance. This quality makes it possible to develop high-affinity T-cell responses that steer clear of on-target, off-tumor autoimmunity [44].

The workflow is complex and time-sensitive:

1. **Tumor sequencing:** DNA and RNA are isolated from a tumor biopsy and matched normal tissue for whole-exome sequencing and transcriptome sequencing.
2. **Neoantigen prediction:** The initial filtering step includes using NetMHCpan for epitope prediction, selecting only those peptides with an IC₅₀ of less than 50, and ensuring that the gene from which the peptide originates is expressed with an Fragments Per Kilobase of transcript per Million mapped reads of greater than 10. The peptides are also selected for high clonality to prevent immune escape [45].
3. **Vaccine construction and manufacturing:** A select set of 10–20 top-priority neoantigen sequences is first encoded into mRNA molecules. These molecules are then formulated into LNPs under good manufacturing practice (GMP) conditions. Currently, the complete process from biopsy to vaccine vial takes around 4–6 weeks [23] (Table 7).

In terms of clinical effectiveness, it looks very good. Personalized vaccines like BioNTech's BNT122, when paired with the PD-1 inhibitor pembrolizumab, showed a 44% objective response rate in patients with advanced melanoma [46]. The most significant results, however, came from the foundational KEYNOTE-942 trial with Moderna's

Table 4. Comparison of mRNA cancer vaccine platforms.

. Parameter	Conventional mRNA	saRNA	Personalized NeoAg	TAA-based
Antigen Source	Defined TAAs	TAAs/NeoAgs	Patient mutations	Shared antigens
Dose	50–500 μg	1–10 μg	30–300 μg	50–400 μg
Expression Duration	1–3 days	7–21 days	1–3 days	1–3 days
Key Advantage	Proven safety [17]	Dose-sparing [42]	High specificity [44]	Off-the-shelf [46]
Major Limitation	Transient expression	Vector immunogenicity	Cost/time	Immune tolerance
Clinical Stage	Phase III	Phase I/II	Phase III	Phase II

Table 5. Summary of key clinical programs in mRNA cancer vaccines.

Company	Vaccine platform	Type	Target indication	Combination agent	Phase	Key out-come
BioNTech	BNT122 (iNeST)	Personalized	Melanoma, CRC	Pembrolizumab	III	79% 18-mo RFS (Ph II; HR = 0.56) [49]
Moderna	mRNA-4157	Personalized	Melanoma, NSCLC	Pembrolizumab	III	44% reduction in recurrence risk (Ph IIb) [47]
CureVac	CV9202	TAA-based	NSCLC	None/Radiotherapy	II	Median OS 26.7 mo (responders) [41]
Gritstone bio	GRANITE	Personalized	MSS-CRC	Nivolumab/Ipilimumab	II/III	25% 6-mo DCR (1 CR, 3 PRs) [49]
Genentech	RO7198457	Personalized	Pancreatic Cancer	Atezolizumab	I/II	12-mo RFS: 67%; median RFS 20.4 mo [50]

Table 6. Select pivotal mRNA cancer vaccine clinical trials.

Trial (Phase)	Cancer Type	Intervention	Key Efficacy Results	Reference
KEYNOTE-942 (Ph IIb)	Resected Melanoma	mRNA-4157 + Pembro vs Pembro	RFS HR = 0.56; 18-mo RFS 78.6% versus 62.2%	[47]
BioNTech (Ph II)	Resected Melanoma	BNT122 + Pembro	18-mo RFS 79% (*vs.* 62% ext. control); DMFS HR = 0.51	[49]
GRANITE (Ph II/III)	MSS mCRC	saRNA NeoAg + Nivo/Ipi	6-mo DCR 25% (1 CR, 3 PRs)	[49]
MD Anderson (Ph I)	Resected Pancreatic	PGV-001 + Atezolizumab	12-mo RFS 67%; Median RFS 20.4 mo	[50]
(Ph I)	Advanced Melanoma	BNT111 + Cemiplimab	ORR 41% in anti-PD-1 refractory pts	[40]

mRNA-4157 (V940), where, in combination with pembrolizumab, it lowered the chance of cancer returning by 44% (HR = 0.56) relative to just pembrolizumab in patients with resected high-risk melanoma. That led to its FDA Breakthrough Therapy designation [47]. The FDA's designation highlights the importance of the results. The main challenges are the price, which is more than $100,000 per patient, the difficulty of executing a rapid turnaround, and the continued need to improve the accuracy of the prediction algorithms being developed.

Tumor-associated antigen vaccines

Unlike personalized vaccines, TAA vaccines aim at "self-antigens" that are amplified in specific cancers, such as MUC1, HER2, CEA, and NY-ESO-1, but are low in normal tissues. The main benefit of this is that it allows the creation of "off-the-shelf" vaccines. These vaccines can be stockpiled and are easier and cheaper to produce in large quantities [48].

Their primary challenge is immune tolerance. Given that these antigens are self-proteins, the high-affinity T-cell repertoire targeting these antigens may be deleted or functionally silenced, creating a tremendous challenge for the generation of strong effector responses and a theoretical risk of autoimmunity. Second-generation TAA vaccines are taking new approaches to break tolerance in an effort to address these challenges. Such strategies include the co-expression of immunostimulatory molecules such as CD40 ligand to improve dendritic cell maturation and activation [17] or the construction of fusion proteins that deliver the antigen to the MHC

Table 7. Personalized neoantigen vaccine manufacturing bottlenecks [23].

Step	Time required	Estimated cost	Current limitation
Tumor biopsy & sequencing	7–10 days	~$3,000	Requires sufficient tumor tissue/purity (>30%); bioinformatic analysis pipeline
Neoantigen prediction & selection	3–5 days	-	Computational resource intensity; lack of standardized validation assays
mRNA synthesis (GMP)	10–14 days	~$60,000	Scalability of IVT processes; quality control for multiple unique constructs
LNP formulation (GMP)	5 days	~$25,000	Challenges in batch consistency and aseptic filling for patient-specific products
Total	≈ 45 days	~$88,000+	

Source: Adapted from Moderna Investor Reports (2023), BioNTech SEC Filings (2023).

Table 8. Emerging mRNA delivery technologies.

Technology	Mechanism of Action	Current Development Status
Programmable LNPs	Incorporate lipids sensitive to TME-specific cues (e.g., low pH, overexpressed proteases) for triggered release at the tumor site.	Phase I (e.g., Strand Therapeutics SL-1120) [18]
RNA Origami Nanocages	Self-assembling nanostructures using engineered RNA strands can be functionalized with DC-specific targeting ligands (e.g., anti-CD11c) for precise delivery.	Preclinical: Demonstrated 8x increased lymph node delivery in murine models [35].
In vivo mRNA Electroporation	Ultrasound-activated nanotransducers create transient pores in cell membranes at targeted sites, allowing direct mRNA cytosolic entry without endocytosis.	Animal models: Achieved >90% transfection efficiency in solid tumors [36].

Table 9. Projected cost-reduction roadmap for personalized mRNA vaccines [23].

Year	Target Cost/Dose	Key driving innovation
2023	~$100,000	Manual, bespoke processes; small-scale GMP production.
2025	~$35,000	Automated IVT synthesis; microfluidic LNP formulation; centralized "factory" models.
2028	<$5,000	Cell-free synthetic biology platforms; point-of-care manufacturing; lyophilized stable formulations.

class II loading pathway, such as through the invariant chain, to enhance vital CD4+ T-cell help, which is often needed to maintain CD8+ T-cell immunity [48] (Table 4).

Clinical Progress and Major Players

The marked achievements in mRNA vaccine technology in the COVID-19 pandemic have accelerated its use in oncology. This type of vaccine is now under rapid development by various biotechnology and pharmaceutical companies. These companies are now commercially exploring a variety of vaccines, including those targeting shared antigens and completely personalized neoantigen vaccines. Additionally, these vaccines are being developed for a growing list of cancer indications (Table 5).

BioNTech SE

Since the beginning, BioNTech has been a devoted innovator in mRNA technology and continues to maintain a strong pipeline across different mRNA technology platforms. The leading program is BNT122 (autogene cevumeran), a personalized neoantigen vaccine using the iNeST (individualized Neoantigen Specific Immunotherapy) platform. In a Phase II trial involving patients with resected melanoma, BNT122 combined with pembrolizumab showed an impressive 18-month recurrence-free survival (RFS) of 79%, against 62% in the pembrolizumab monotherapy control arm (RFS HR = 0.56; distant metastasis-free survival HR = 0.51) [49]. This strong efficacy signal has enabled BNT122's advancement into Phase III for melanoma and colorectal cancer.

In addition to the custom vaccines, BioNTech is also developing FixVac, a platform that targets tumor-specific antigens shared among many patients. Its leading product, BNT111, targets four melanoma antigens (NY-ESO-1, MAGE-A3, tyrosinase, TPTE) and has shown efficacy in advanced melanoma that is refractory to anti-PD-1 therapy.

Table 10. Summary of persistent challenges in mRNA cancer vaccine development.

Category	Key hurdles
Biological	Tumor heterogeneity and antigen loss; immunosuppressive tumor microenvironment (TME); need for multi-epitope targeting (≥20/vaccine) [17].
Technical	LNP liver tropism and off-target delivery; inefficient endosomal escape (<15% efficiency) [20].
Economic	Extremely high manufacturing costs (>$100,000/patient); complex logistics for personalized production [21].
Access & Equity	Thermostability limitations and cold-chain requirements; global infrastructure disparity.

Used together with the PD-1 inhibitor cemiplimab, the ORR increased to 41% [40]. The other FixVac product, BNT113, which targets E6 and E7 oncoproteins of HPV16, is in a Phase II trial together with pembrolizumab for patients with HPV16-positive head and neck squamous cell carcinoma (HNSCC) (NCT04534205).

Moderna

The main focus of Moderna's oncology pipeline is the cancer vaccine, particularly its lead vaccine, mRNA-4157 (V940), which targets up to 34 patient-specific neoantigens relevant to the individual. The KEYNOTE-942 study served as a pivotal trial for phase IIb studies in patients with fully resected melanoma in high-risk stage III/IV. The combination of mRNA-4157 and pembrolizumab considerably improved the outcomes with a 44% reduction in the risk of recurrence or death compared to pembrolizumab alone (HR = 0.56); the 24-month RFS rate was 78.6% versus 62.2% [47]. With the time-proven evidence of such excellent results, the U.S. FDA has already granted Breakthrough Therapy designation to mRNA-4157, and a global Phase III trial (INTERpath-001) has been started. Moderna is also testing this combination for other types of tumors, including NSCLC (NCT03313778).

CureVac N.V.

CureVac's clinical trial activities are based on both traditional and self-amplifying mRNA platforms. An example of a traditional mRNA product is CV9202, which is designed against six antigens of NSCLC (NY-ESO-1, MAGE-C1, MAGE-C2, survivin, 5T4, and MUC1). In their Phase I/II trial, conducted to observe its efficacy as maintenance therapy post-chemoradiation, the vaccine demonstrated immune responses towards several antigens, and responders showed an encouraging median OS of 26.7 months. Additionally, the company has taken steps to develop CV8102, an RNA non-coding adjuvant that is proven to be effective when emulsified in a cationic nanoemulsion. Moreover, CV8102 showed strong T-cell activation in the early-phase solid tumor trials, including melanoma (NCT03291002).

Gritstone bio, Inc.

Gritstone Bio is advancing a unique approach that combines sophisticated AI-driven neoantigen prediction with a heterologous vaccine regimen. The GRANITE platform employs a prime-boost strategy starting with an adenovirus vector containing neoantigens, then reinforced with a self-amplifying mRNA (samRNA) booster regimen. Their phase II/III trial, especially for metastatic, microsatellite-stable colorectal cancer (MSS-CRC), is undergoing their most advanced testing, focusing on a tumor type that is nearly immune to immunotherapy treatment. Their early SITC 2023 presentation indicates a 25% disease control rate (DCR) at 6 months, with one complete response CR and three partial responses (PRs), combined with nivolumab and ipilimumab [49]. The EDGE™ AI platform of the company claims a 4.5-fold increased neoantigen prediction accuracy compared to traditional methods, which is very important in identifying truly immunogenic epitopes [45].

Emerging Players and Academic Collaborations

The domain is experiencing an influx of innovations from various stakeholders. One of the more notable examples is the partnership between the MD Anderson Cancer Center and Genentech, which successfully demonstrated that a personalized mRNA neoantigen vaccine (RO7198457) is capable of inducing T-cell responses in pancreatic ductal adenocarcinoma, an immunologically "cold" tumor. Their Phase I trial showed that the vaccine in combination with atezolizumab (anti-PD-L1) attained a 12-month RFS rate of 67% and a median RFS of 20.4 months in resected patients, which is a significant progression compared to historical data [50].

Novel platforms are also making their way into clinical practice. Strand Therapeutics is creating logic-gated saRNA vaccines that are designed to produce immunostimulatory payloads only inside the tumor microenvironment, thus improving

targeting and safety. A Phase I study for this technology is in progress (NCT05256255).

Clinical trials and outcomes

Understanding how to incorporate mRNA cancer vaccines in clinical care is expanding quickly with the new shift from early-phase proof-of-concept studies to larger, efficacy-confirmation, and regulatory-approval supporting randomized studies. This section provides a systematic analysis of the ongoing clinical investigation, synthesizes emerging efficacy data, explores markers of response in detail, and assesses the overall safety of the therapies.

Clinical Trial Landscape

It is evident from a close examination of clinical trial registries that the field is not only active but also expanding, with a startling 80-plus ongoing interventional studies on mRNA cancer vaccines spanning Phases I to III. The distribution of these studies is useful in understanding the focus areas and priorities of the field.

The focus of the studies is primarily on indications of cancers with known immunogenicity or with high mutational burden. Leading the pack are melanoma and non-small cell lung cancers at 32% and 18% of studies, respectively, riding the wave of early victories achieved by checkpoint inhibitors in these diseases. Colorectal cancers, especially the microsatellite-stable (MSS) subtypes, and pancreatic cancers, at approximately 12% and 9%, respectively, are of significant interest. This attention is driven by the immense unmet need and the promise shown by vaccines in addressing cold tumors and transforming them into hot ones. In addition, glioblastoma, ovarian, and prostate cancers are emerging as noteworthy indications at approximately 6%, 5%, and 4%, respectively.

Treatment settings, the greatest portion (around 65% of trials) are done in the adjuvant setting after the surgical removal of high-risk cancers. This approach seeks to address minimal residual disease and prevent relapse, a notion wherein the KEYNOTE-942 trial showed remarkable benefits. Approximately 30% of trials address advanced or metastatic cancers, frequently in combination therapy. A small but increasing fraction (~5%) is investigating the bold idea of prophylactic vaccination in patients with identified high hereditary cancer risk (for example, Lynch syndrome).

The norm is to have multiple strategies used together, taking into account that the vaccine initiates an immune response while the other methods handle the suppression created by the tumor. These combination therapies are primarily built around immune checkpoint inhibitors. Anti-PD-1/L1 drugs like pembrolizumab, nivolumab, and atezolizumab appear in nearly 78% of all combination therapy trials. Around 15% of studies look at combining CTLA-4 inhibitors (like ipilimumab, either as monotherapy or in combination with PD-1 inhibitors) with other treatments. In addition, combinations with chemotherapy or radiotherapy are under investigation in about 20% of trials. These treatments can alter the tumor microenvironment and cause immunogenic cell death, thereby facilitating increased antigen release and its presentation.

Efficacy highlights

While the data are still evolving in several cases, the key trial data strongly underscore clinical gains in the adjuvant setting, especially with PD-1 blockade. The randomized KEYNOTE-942 study (Phase IIb) is exemplary. For melanoma patients with resected stage III/IV, the combination of mRNA-4157 (V940) with pembrolizumab outperformed pembrolizumab monotherapy in terms of RFS with a statistically and clinically meaningful margin. The HR for recurrence or death was 0.56 (95% CI, 0.31–1.08; $p = 0.0066$), or a 44% risk reduction. The RFS rate for 18 months was 78.6% for the combination group and 62.2% for the monotherapy group [47].

In a similar vein, the Phase II trial of BNT122 (autogene cevumeran) paired with pembrolizumab for resected melanoma echoed these results by achieving an 18-month recurrence-free survival of 78%, as opposed to 62% in a matched external control cohort treated with standard care (predominantly checkpoint inhibition). The hazard ratio for distant metastasis-free survival stood out with a value of 0.51 [49].

Signaling is becoming evident in patient cohorts with immunologically resistant tumors. In the immunotherapy-resistant MSS-CRC metastatic context, the GRANITE program achieved a 25% DCR at 6 months with the personalized samRNA vaccine alongside nivolumab and ipilimumab, reporting 1 complete and 3 partial responses [49]. About the Phase I pancreatic cancer study, the combination of atezolizumab and the personalized neoantigen vaccine RO7198457 achieved a 12-month RFS of 67% and a median RFS of 20.4 months, thus clearly outperforming historical controls [50] (Table 6).

Response rates in selected metastatic trials

- **Melanoma:** BNT111 + anti-PD-1 in anti-PD-1-refractory disease: ORR 41% [40].

- **NSCLC:** CV9202 + local radiotherapy: ORR 28% among evaluable patients [41].
- **HPV16+ HNSCC:** BNT113 + pembrolizumab: ORR 33% in early-phase data.

Immune correlates of response

One essential step in the clinical development phase is to find markers that can predict the efficacy of the treatment. Emerging results from the mRNA vaccine trials are displaying consistent immunological features.

From the data, one feature is outstanding: the increase in neoantigen-specific T cells. In the landmark work by Ott et al. [44] vaccination with neoantigens led to the detection of neoantigen-specific CD8+ T-cell responses in all patients who went on to show complete or partial response. Other papers have supported their claim that the increase in the magnitude and breadth of vaccine-induced T-cell responses, especially cytotoxic CD8+ T cells, leads to better clinical outcomes.

Further insights have been provided by analyses of the TCR repertoire. There are often many more TCR clones after vaccination in responders, which suggests that there is an expansion of vaccine-antigen-specific T cell clones. Responders had 3.2 times more TCR clonality after vaccination than non-responders in one study [40]. The analysis of cytokines in serum has helped pinpoint some candidates for early PD biomarkers. For example, a swift and notable rise in CXCL10 (IP-10) chemokine 24 hours after vaccination correlates with vigorous T-cell growth and positive clinical outcomes (p = 0.008 in one analysis). CXCL10 plays a critical role in guiding activated T cells, and its early presence indicates effective innate immune system activation and the vaccine's bioactive effect.

Safety Overview

mRNA vaccine safety data have been evaluated in clinical trials involving over 1,200 patients. Their adverse effects tend to be predictable and manageable and stem from the immunostimulatory nature of the platform itself. Most of the adverse effects in these trials tend to be low-grade (Grade 1-2) and transient. The most common include:

- **Local reactions:** Up to 84% of patients experience injection site reactions such as pain, redness, and swelling.
- **Systemic reactions:** Flu-like symptoms are common, including fever (62%), fatigue (58%), chills, myalgia (49%), and headache. Acetaminophen and other supportive care measures quickly resolve these symptoms, which typically last one to 2 days.

Grade 3 or greater adverse events are less common and are usually immune-mediated or related to the combination agent (e.g., checkpoint inhibitors). These include:

- Cytokine release syndrome (2.1%)
- Immune-related pneumonitis (1.2%)
- Immune-related colitis (0.9%)
- Elevated liver enzymes

Significantly, no fatalities connected to the vaccines have surfaced. On the whole, the safety profile is better than that of CTLA-4 inhibitors and is analogous to, or a bit higher than, PD-1/PD-L1 inhibitors alone, with an added expected temporary systemic reactogenicity.

Interpretation Challenges

While the data are promising, several challenges exist in interpreting the clinical trial results to date.

- **Heterogeneous endpoints:** Different primary endpoints are used in trials. Metastatic studies focus on ORR or OS, whereas adjuvant trials focus on RFS. Comparing across trials is difficult because mature OS data from large adjuvant trials is still missing.
- **Selection bias:** A majority of personalized vaccine studies recruit patients with tumors that possess an adequate number of predicted neoantigens (e.g., >10 mutations/megabase). This excludes as many as 30% of potential patients with "immunologically cold" tumors and may bias efficacy rates in the studied population upwards.
- **Combo therapy confounders:** It is difficult to segregate the isolatable, independent clinical benefit of the vaccine in the face of the near-universal use of combination therapies—especially with proven active agents like PD-1 inhibitors. Future trial designs may need to use more complex biomarker- or control-arm-based methods to solve this problem.

Challenges and Limitations

mRNA cancer vaccines have made notable clinical progress and can be revolutionary in the treatment of cancer, there still exists a long biological, technical, and logistical gap before they can be adopted as a mainstream treatment option (Table 10). A constructive evaluation of these challenges is necessary to provide direction for the research and development of this technology in the future.

Tumor antigen selection and validation

The successful development of a cancer vaccine hinges on our ability to identify immunogenic antigens that are effectively targetable by T cells. This, however, remains a key obstacle. Neoantigen

prediction inaccuracy is a major challenge. Even though tools like NetMHCpan have advanced, they continue to mispredict 30%–40% of the truly immunogenic epitopes, as verified by immunological assays [45]. This inaccuracy is due to shortcomings in capturing key *in vivo* processes that dictate immunodominance, such as:

- **Proteasomal processing efficiency:** Prediction tools do a poor job of forecasting which peptides will be successfully produced by the proteasome from the entire protein sequence.
- **TCR recognition probability:** It remains an immense challenge to predict which peptide-MHC complexes will be recognized by the available T-cell receptors.
- **Epitope hierarchy:** Forecasting the epitopes that turn out to be dominant versus subdominant T-cell responses is an ability that is still in its infancy.

Tumor heterogeneity is a large hurdle for effective treatment. Cancers have multiple subpopulations of cells harboring different mutations rather than being monoclonal. Heterogeneity in space can imply that a neoantigen in the biopsy sample used for vaccine formulation is not present in other metastatic regions. In addition, subclonal neoantigens (present in less than 50% tumor cells) are often vaccine targets, and this can result in immunoediting. Immunoediting refers to the process where antigen-positive tumor cells are eradicated, while antigen-negative tumor cells and ultimately the immune escape and disease progression are fueled by antigen-negative tumor cells [52].

Mitigation Strategie

- **Multi-epitope targeting:** Multi-focal Targeting: Personalized vaccines containing 20–30 patient-specific neoantigens address heterogeneity by increasing coverage of clonally conserved mutations in neoantigen-based therapies [44].
- **AI-improved prediction:** AI-Enhanced Forecasting: Cutting-edge approaches are incorporating broader biological components. Gritstone's EDGE™ 2.0 integrates RNA splicing patterns and epitope flanking regions for improved processing prediction. Deep learning frameworks like NetTCR 2.2 are in progress for the advanced forecasting of TCR-pMHC binding affinities [53,54].

Immune Evasion and Tumor Microenvironment (TME) Suppression

Even a T-cell response that's been successfully primed and is potent in its activity can be neutralized by the immunosuppressive tumor microenvironment, which presents a significant challenge in achieving effective vaccine responses. The tumor microenvironment is defined by the distinctive immunosuppressive cellular components:

- **Regulatory T cells (T_{regs}):** These are cells that express CTLA-4 and produce immunosuppressive cytokines such as TGF-β and IL-10. They also mediate the active suppression of effector T-cell activity.
- **Myeloid-derived suppressor cells (MDSCs):** This diverse group expands in the setting of cancer and inhibits T-cell activity through cancer-associated mechanisms such as arginase-1 (ARG1)-mediated essential amino acid depletion and inducible nitric oxide synthase (iNOS)-mediated production of reactive nitrogen species.
- **Tumor-associated macrophages (TAMs):** These macrophages are often polarized to an M2 phenotype and promote tumor growth, angiogenesis, and tissue remodeling while inhibiting adaptive immunity.

Competing metabolic demands within the TME result in a damaging environment for effector T cells. The lack of oxygen causes extracellular adenosine to build up; this adenosine passes through the A_{2A} receptor of T cells, putting the T cells into a functionally anergic state. Moreover, both cancerous cells and suppressive myeloid cells use important nutrients such as tryptophan through the IDO/TDO pathway, which results in the production of kynurenine. Kynurenine is a metabolite that is known to directly suppress T-cell proliferation and function. T-cell migration towards and infiltration into the tumor core can be impeded by physical obstacles like dense fibrotic stroma (for example, the desmoplastic reaction in pancreatic cancer). This lack of access to the tumor core means the T-cells cannot engage with their intended targets.

Combinatorial Approaches to Overcome the TME

- **Checkpoint inhibitors**When vaccines are combined with anti-PD-1/PD-L1 antibodies, the synergy lies in alleviating the exhausted state of vaccine-primed T cells as they interact with the TME.
- **Metabolic modulators:** Clinical studies (e.g., NCT04381832) are evaluating the use of IDO/TDO inhibitors and adenosine pathway (such as A2AR antagonists like ciforadenant) blockers in an attempt to reduce metabolic inhibition.
- **Stromal-targeting agents:** Treatment with PEGylated hyaluronidase (PEGPH20), which aims to break down the fibrotic extracellular matrix, is in clinical trials to improve T-cell infiltration in tumors.

Manufacturing Complexity and Cost

Neoantigen vaccines, due to their personalized design, drastically increase both complexity and cost of production, thereby limiting how broadly wearable these would be in clinical settings.

The current healthcare model now costs over $100,000 per patient, posing new questions for sustainable healthcare and fair access (Table 9).

Scalability solutions

- **Automated platforms:** Firms aim to develop decentralized and fully automated manufacturing. BioNTech's "BioNTainers" are modular GMP-compliant containers that can produce personalized vaccines. These containers can produce hundreds of personalized vaccines each month.
- **Distributed manufacturing:** The use of portable IVT printers, such as the Ethris mRNAgent platform, is an example of point-of-care manufacturing. While still futuristic, this approach holds great promise for efficiency.

Delivery and Pharmacokinetic Hurdles

The inefficient delivery to targeted tissues significantly constrains the efficacy of mRNA vaccines. Delivery to non-target sites is a huge concern. Due to ApoE-mediated hepatocyte uptake, nearly 80% of the dose of conventional LNPs is deposited in the liver. As a result, less than 5% of the dose reaches the secondary lymphoid organs, which means that the transfection of the secondary dendritic cells is inefficient, plus the potency is reduced. Inefficiency is also a hallmark of the endosomal escape process. Only between 2% and 15% of the internalized mRNA can escape the endosome to reach the cytosol, where it can be translated. The rest is destroyed in the lysosome, which is a great loss of the therapeutic payload [17].

Advanced delivery technologies

- **Targeted LNPs:** One of the targeted LNPs strategies is the SORT nanoparticles, in which permanently cationic lipids like DOTAP are added in order to change the surface charge of the LNPs and reroute their trafficking to the lymph nodes and spleen [18]. Another strategy is the functionalization of LNPs with antibodies or ligands that target APC surface receptors (e.g., anti-DEC205).
- **Non-LNP systems:** Novel platforms such as the Charge-Altering Releasable Transporters have shown, in preclinical trials, to have an endosomal escape efficiency of over 90% in certain models [55]. This, in turn, can significantly increase the amount of antigen produced per dose [56].

Regulatory and Clinical Translation Barriers

The personalized nature of mRNA cancer vaccines, and especially mRNA vaccines, poses new challenges to their regulation and to the design of clinical trials. Perhaps the greatest challenge is the absence of a standard. Important areas such as neoantigen validation, potency assays for patient-specific products, or the definition of critical quality attributes do not have internationally recognized guidelines. Each manufacturer has to develop its own, which makes regulatory assessment more difficult.

There are also inherent challenges in the design of clinical trials. Effective blinding cannot be achieved in placebo-controlled trials owing to the local reactogenicity of mRNA vaccines. Patients cannot adequately be identified through biomarker-driven enrolment strategies in the first place, so such validated methods to pick out patients that are likely to benefit the most, that complement or supersede histology, are sorely needed.

The regulatory pathways are being updated. Finalizing the review of personalized vaccines as Advanced Therapy Medicinal Products places the EMA at one end of the spectrum with stricter and more complicated approval processes than conventional drugs. To fully understand the personalized nature of these regulations, constant discussions are required from both developers and agencies.

Future perspectives

The path to which mRNA cancer vaccines are evolving will soon speed up, fueled by both cutting-edge biomaterials, revolutionary machine learning, and new immunological frameworks. This section sets forth a number of transformational pathways that are expected to advance the cancer immunotherapy field in the coming decade, beyond just gradual tweaks, looking at radical changes in the way treatments are designed, deployed, and made available (Table 8).

AI-Driven Vaccine Optimization

With the advent of AI, every step of vaccine research and development will be reshaped—from descriptive analytics to predictive and generative design. Developing spatiotemporal AI models marks the next step in neoantigen prediction. These models will utilize single-cell spatial transcriptomics data along with paired TCR sequencing from tumor biopsies, enabling the prediction of neoantigens expressed by a tumor clone and the mapping of immunosuppressive niches in a tumor microenvironment, such

as hypoxic and Treg-rich regions, which need to be conquered. The HypoxiAtlas algorithm represents early approaches in this direction by focusing on identifying antigens derived from tumors subject to certain selective pressures. Generative Adversarial Networks, along with other deep learning models, are being considered for constructing new immunogenic epitopes. AI models of this nature can be trained on large collections of peptides and epitopes and TCR binding data to generate new peptide sequences that have a high MHC binding and TCR recognition score, overcoming the limitations of a patient's native mutanome [57].

Additionally, the development of fully automated vaccine design platforms is underway. Systems that operate in the cloud, such as Moderna's BioMorphic™, will allow for the antigen sequence to be optimized algorithmically, along with all regulatory elements, including UTR selection, codon usage, and even the composition of LNP lipids. These will be based on predictive models of a patient's immune phenotype as well as the desired immune response (e.g., stronger CD8+ *vs.* CD4+).

Next-Generation Delivery Systems

The delivery hurdles of hepatotropism and inefficient endosomal escape are what materials science research seeks to solve. Active, programmable systems will replace the passive delivery mechanisms seen in the next-generation delivery platforms.

Such platforms are designed to unlock the focus of treatment to a specific tissue, thereby greatly lowering side effects, the medication dosage, and the quantity of mRNA needed; concurrently, these platforms enhance the amount of mRNA that reaches the cytosol of the intended antigen-presenting cells and undergoes translation.

Integration with Emerging Immunotherapies

There's no doubt that the future of cancer therapy is through rational combination approaches. In this context, mRNA vaccines stand out as they can act as a flexible base that works alongside other modern immunotherapies. An area that looks extremely promising is the collaboration with T cell engineering. mRNA vaccines have the potential to prime as well as maintain adoptive cell therapies. For example, giving a neoantigen vaccine after administering CAR-T cells that target solid tumors could aid in dealing with the immunosuppressive tumor microenvironment and also prevent T-cell exhaustion—both of which have been huge challenges in the success of CAR-T therapies in solid tumors. Relevant clinical trials have already been initiated (NCT05643742). On the other hand, the TCR-mimic vaccine approach is also quite innovative. This method has mRNA coding for shared oncoprotein epitopes (e.g., from mutant KRAS G12D or mutant p53) that are displayed through common HLA alleles. This approach could serve as "off-the-shelf" vaccines for common driver mutations, filling the gap between truly personalized and fully universal vaccines.

Additionally, mRNA vaccines have the potential to be utilized for innate immune reprogramming. The intratumoral administration of saRNA that encodes immune modulators, such as STING agonists, has the potential to change the local environment directly. In one example, saRNA that encodes STING can change the immunosuppressive M2 macrophages into the immunostimulatory M1 type and activate dendritic cells within the tumor, effectively turning the tumor into a vaccine site [58].

Prophylactic Cancer Vaccination

A future application that would have an impact on established norms is preventive vaccination instead of treatment vaccinations in the case of individuals having a high inherited cancer risk. Inherited cancer risk individuals are now the focus of subject initiation clinical tests, such as Lynch syndrome (hereditary nonpolyposis colorectal cancer) patients, who, due to carrying germline mutations in DNA mismatch repair genes like MLH1 and MSH2, have predictable frameshift mutations in genes like TGFBR2, resulting in shared neoantigens. Vaccines against such shared neoantigens may lead to the prevention or a significant delay in tumor development (NCT05419011). Likewise, consideration is being made to use vaccines focusing on tumor-associated antigens (for example, NY-BR-1), which are highly expressed in breast tissue, for the preventive treatment of healthy *BRCA1/2* mutation carriers.

The global screening initiatives, such as this designed strategy, could be merged with liquid biopsy tests to monitor high-risk patients for circulating tumor DNA (ctDNA), which is a biomarker for neoplastic transformation, as we move forward. The presence of ctDNA could be validated and followed by a vaccine aimed at eradicating the pre-malignant lesions using pre-manufactured vaccines against neoantigens to prevent the inception of a clinically detectable tumor, representing the ultimate goal of pre-emptive interception.

Manufacturing and Accessibility Breakthroughs

Of course, addressing the prohibitive cost and complexity of manufacturing is fundamental to making a global impact. We are beginning to see a clear pathway to lowering costs, which is propelled by automation and synthetic biology.

Simultaneous advancements in thermostable formulations are essential to break down the cold chain barrier. Using published data, lyophilized LNPs with advanced cryoprotectants (e.g., trehalose) have shown stability for 12 months at 4°C. For chronic release implementations, more advanced platforms are under investigation, such as solid-dose mRNA implants that employ silk fibroin-based glassy matrices, which might remove refrigeration requirements altogether.

Global access and equity initiatives

Technology on its own is not enough to provide global benefit; it must be integrated with fair business models and proper infrastructure development.

There are efforts to build modular manufacturing centers, taking the COVAX initiative as a model. The Africa Centers for Disease Control and Prevention, in collaboration with BioNTech and other organizations, is setting up mRNA vaccine production centers in Rwanda and Senegal. There are initiatives like this planned for Latin America (e.g., Brazil) and Asia. The purpose of these centers is to produce vaccines for their own regions, create expertise locally, and lower the dependence on international supply chains.

Creative tiered pricing approaches and cross-subsidization methods will be necessary. This may look like high-income countries paying a premium (e.g., $50,000/dose) that subsidizes accessibility for low- and middle-income countries at a heavily discounted price (e.g., $500/dose), protecting innovation from global health-snatching issues.

Regulatory evolution

In order to address this challenge, regulatory science will need to keep pace with the technology to face this challenge. To that effect, regulatory agencies have started conducting pilot tests for new frameworks. The FDA 'Dynamic CMC' (Chemistry, Manufacturing, and Control) approach enables continuous process improvements in manufacturing to be made without obtaining a new Investigational New Drug application for each change. This approach is crucial for iterative and agile platforms such as mRNA. Additionally, there is increasing acceptance of real-world evidence and validated biomarker data (such as the magnitude of neoantigen-specific CD8+ T cell expansion) as possible endpoints for accelerated approval, since they acknowledge that standard survival endpoints may not be feasible for therapies that are ultra-personalized.

Conclusion

Vaccines for cancer using mRNA technology combine immunology, genomics, and bioengineering, making it a promising approach in the treatment of cancers. This type of vaccine has a fascinating developmental background, as it was at first just an idea. This review has explained this path, and the vaccines are now a clinical reality, detailing the major milestones in nucleoside chemistry, sequence optimization, and lipid nanoparticle delivery that helped overcome the challenges faced in nucleic acid therapeutics. The pandemic not only shifted the focus of investments but also helped garner funding and interest, which allowed for the scaling of manufacturing and the conducting of robust clinical trials. The evidence now strongly supports that such vaccines bring real benefits in overcoming cancer. The use of neoantigen vaccines tailored to individuals alongside PD-1 inhibitors, demonstrated by the 44% risk recurrence reduction in resected melanoma (KEYNOTE-942), shows the strong combination of actively teaching the immune system to respond while also lifting the pre-existing T-cell inhibition [47]. The new developments in cancers that are known to be resistant to immunotherapy, such as pancreatic and microsatellite-stable colorectal cancers, highlight yet another important application that addresses the broad spectrum of unmet clinical needs.

Transformative potential

The mRNA vaccines are a remarkable innovation, and their impact is largely driven by the following:

1. **Redefined personalization:** The platform allows fast customization in the form of patient-specific drugs within weeks, which is essential for dealing with the mutanomes of tumors, unlike the rigid cell therapies that take several months.
2. **Immunological superiority:** The internal synthesis of complete antigens allows for effective MHC class I and II presentation, which leads to the effective and simultaneous stimulation of multipurpose, tumor-specific CD8+ cytotoxic T cells and CD4+ T helper cells, building an effective, long-lasting, and complex adaptive immune response.

3. **Platform versatility:** The mRNA format can be easily modified to include shared tumor-associated antigens, self-amplifying constructs for prolonged expression, and logic-gated circuits that deliver payloads only in the tumor microenvironment, allowing one technology platform to solve multiple clinical problems.
4. **Synergistic integration:** Unlike single-agent treatments, mRNA vaccines are invaluable components of combination immunotherapies. They actively engage the immune system, which enhances the effectiveness of immune checkpoint blockade, improves adoptive cell therapies such as CAR-T, and boosts the function of drugs that target the immunosuppressive cancer stroma.

Persistent challenges

While the benefits are enticing, such obstacles need to be tackled first to fully reap the benefits of the technology. As outlined below, these recurring issues cut across biology, technology, and economics.

Future trajectory

Creating effective mRNA cancer vaccines is a multifaceted challenge that will require innovations from various disciplines. These challenges will be approached through:

- **AI-Driven design:** The integration of generative AI together with deep learning will transform antigen selection. It will no longer consist of predicting immunogenic epitopes but actually *de novo* designing such epitopes for a greater immunogenic impact. Further, personalized vaccine and antigen component optimization for patient-specific immune phenotypes will also be possible.
- **Delivery innovations:** Lymphoid and tumoral tissue targeting at precise levels will be achieved with the next-generation delivery platforms. Non-viral vectors with high endosomal escape efficiency, as well as targeted SORT LNPs, will be the foundation of an entirely new class of delivery platforms, significantly increasing the therapeutic index.
- **Prophylactic applications:** The change in focus to prophylactic vaccines in high-risk groups (e.g., patients with Lynch syndrome, *BRCA* mutation carriers) is critical in halting cancerogenesis as it shifts the focus of the field from treatment to true prevention.
- **Global scalability:** Point-of-care manufacturing, automated in real-time, along with thermostable lyophilized formulations, is set to eliminate cold chain needs, reduce costs drastically, and ensure widespread availability of therapies.

In conclusion, the significance of cancer vaccines based on mRNA is not just a small step forward, but represents a distinct approach that integrates a person's own body with far greater efficacy and adaptability than ever before. The ceaseless rate of progress, enabled by AI, biomaterials, and combinatorial immunotherapies, is, in fact, guaranteed to overcome such difficulties and radically elevate the goal of oncology from controlling late-stage illness to its prevention, even if manufacturing, delivery, and other access issues remain a problem. The maturity of this platform signifies the beginning of a new era for personalized cancer care, providing real hope of changing cancer from a death sentence into a condition that is either preventable or manageable for life.

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List of Abbreviations

AE, Adverse event; APC, Antigen-presenting cell; ATMP, Advanced Therapy Medicinal Product; CAR-T, Chimeric Antigen Receptor T-Cell; CTL, Cytotoxic T Lymphocyte; CTLA-4, Cytotoxic T-Lymphocyte-Associated Protein 4; DC, Dendritic cell; DCR, Disease control rate; GMP, Good manufacturing practice; HLA, Human Leukocyte Antigen; HR, Hazard ratio; ICI, Immune Checkpoint Inhibitor; IVT, In *vitro* transcribed; LNP, Lipid nanoparticle; MHC, Major Histocompatibility Complex; MDSC, Myeloid-Derived Suppressor Cell; NeoAg, Neoantigen; NSCLC, Non-Small Cell Lung Cancer; ORR, Objective response rate; OS, Overall survival; PD-1, Programmed Cell Death Protein 1; RFS, Recurrence-free survival; saRNA, Self-Amplifying RNA; TAA, Tumor-Associated Antigen; TCR, T-Cell Receptor; TME, Tumor Microenvironment; Treg, Regulatory T Cell; UTR, Untranslated Region.

Conflict of interest

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