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mRNA VACCINES AND THEIR ROLE IN MODULATING THE IMMUNE RESPONSE

Esraa Ahmed Abdulqadur

Department of medical lab. College of Medical Techniques, Al-Farahidi University, Baghdad, Iraq.

Email: esraa.abdulqader@uoalfarahidi.edu.iq

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Abstract

Messenger RNA (mRNA) vaccines have transitioned from a research concept of decades to a validated therapeutic platform, accelerated by the rapid development of highly effective vaccines during the COVID-19 pandemic. The hallmark of these vectors is the delivery of genetic instructions, rather than a preformed antigen. The delivered transcript is translated by host cells and the resultant protein is presented to the immune system, thus engaging both the innate and adaptive arms in a manner that closely mimics natural infection . This review summarizes the immunological mechanisms that shape the immune response to mRNA vaccines.

We first describe the molecular architecture of the transcript—the 5′ cap, untranslated regions, open reading frame, and poly(A) tail—and the nucleoside modifications and lipid nanoparticle (LNP) delivery systems that govern its behaviour in vivo. We then examine innate immune sensing by endosomal and cytosolic pattern recognition receptors (TLR3/7/8, RIG-I, MDA5, PKR and the OAS/RNase L system), the pivotal type I interferon response, and the intrinsic adjuvant activity of the LNP carrier. We describe how these signals license dendritic cell maturation and antigen presentation, bridging to the adaptive response: germinal centre formation, T follicular helper and B-cell driven antibody affinity maturation, and $CD4^+$ and $CD8^+$ T-cell programming, culminating in durable immunological memory. Finally, we consider the balance between immunogenicity and reactogenicity, survey applications in infectious disease and personalised cancer immunotherapy, and outline the principal challenges and future directions of the field, including self-amplifying RNA and tolerogenic mRNA design.

Keywords: mRNA vaccine; lipid nanoparticle; innate immunity; pattern recognition receptors; type I interferon; adaptive immunity; germinal centre; neoantigen; cancer immunotherapy; self-amplifying RNA

1. Introduction

Vaccination remains one of the most cost-effective interventions in the history of medicine, yet for most of the twentieth century vaccine development relied on live-attenuated or inactivated pathogens, recombinant subunit proteins, or viral vectors. Each of these approaches carries intrinsic limitations: lengthy and pathogen-specific manufacturing,

cold-chain and biosafety burdens, and, for some platforms, pre-existing immunity against the delivery vehicle. Messenger RNA (mRNA) vaccines were conceived as a way to circumvent these constraints by supplying the host with the genetic blueprint of an antigen and allowing the recipient's own cells to synthesise it [1,6].

This is nothing new. The feasibility of in vitro-transcribed (IVT) mRNA as a template for protein expression after injection was proven in the early 1990s, but two obstacles delayed its clinical translation for more than two decades: the intrinsic instability of the molecule and its powerful, frequently adverse, immunostimulatory properties. The key to this was the realization that native IVT mRNA is detected by innate immune receptors as a danger signal and that the inclusion of naturally occurring modified nucleosides, such as pseudouridine, can reduce this recognition and also improve translation [3,4]. At the same time, advances in lipid nanoparticle (LNP) chemistry addressed the challenge of delivering a large, negatively charged, nuclease-sensitive molecule into the cytoplasm of target cells [2,17]. The combination of these two innovations paved the way for the platform's clinical breakthrough.

The COVID-19 pandemic transformed mRNA vaccines from a promising modality into a proven one. Within a year of the release of the SARS-CoV-2 genome sequence, two mRNA vaccines—BNT162b2 and mRNA-1273—had demonstrated approximately 95% efficacy against symptomatic disease in large randomised trials and were administered to billions of people [10,11,12]. This unprecedented achievement validated not only the safety and efficacy of the platform but also its central promise: speed. Because the manufacturing process is sequence-independent, a new vaccine can, in principle, be designed within days of identifying a target antigen, using an identical production pipeline.

The scientific significance of these advances was formally recognised when the 2023 Nobel Prize in Physiology or Medicine was awarded to Katalin Karikó and Drew Weissman for their discoveries concerning nucleoside base modifications that enabled the development of effective mRNA vaccines against COVID-19—a recognition that underscored how far immunological insight, rather than chemistry alone, determined the platform's success [3,4].

Most importantly, mRNA vaccine success depends on how they interact with the immune system. Compared to a protein subunit vaccine, which provides a whole antigen, an mRNA vaccine transforms the recipient's cells into temporary antigen-producing factories by generating protein that undergoes native folding and post-translational modifications and is presented through both the MHC class I and MHC class II pathways [5]. This intracellular expression, together with the intrinsic immunostimulatory properties of the RNA and its carrier, leads to a balanced response consisting of neutralizing antibodies, T follicular helper (Tfh) cells and cytotoxic $CD8^+$ T lymphocytes. We need to understand precisely how each component of the vaccine contributes to this response, both to interpret clinical outcomes and to engineer the next generation of products. This review therefore emphasizes the immunological mechanisms underlying mRNA vaccines, from the response to the molecular design of the transcript, to innate sensing, and to the development of long-lasting adaptive immunity, before addressing applications and future perspectives.

2. Molecular Architecture and Design of mRNA Vaccines

The performance of an mRNA vaccine is dictated in large part by the design of the transcript itself. An IVT mRNA is engineered to recapitulate the structure of a mature eukaryotic mRNA, comprising five functional elements arranged from the 5′ to the 3′ end: a 5′ cap, a 5′ untranslated region (UTR), the open reading frame (ORF) encoding the antigen, a 3′ UTR, and a poly(A) tail [2, 62, 67]. Each element can be independently optimised to enhance stability, translational efficiency, and—where desirable—immunogenicity.

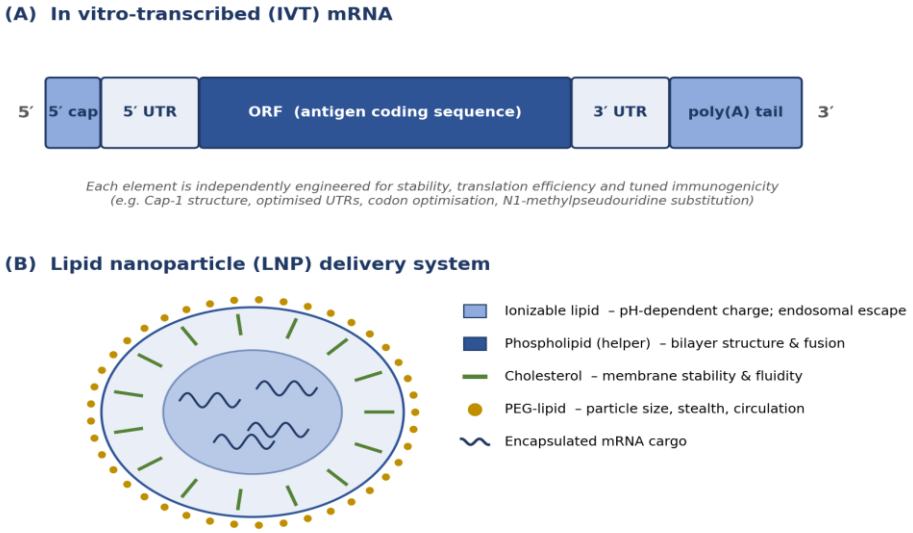


Fig. 1. Molecular architecture of an mRNA-LNP vaccine. (A) The in vitro-transcribed transcript comprises five functional elements—the 5′ cap, 5′ untranslated region, open reading frame encoding the antigen, 3′ untranslated region, and poly(A) tail—each independently engineered. (B) The lipid nanoparticle carrier is a four-component formulation (ionizable lipid, phospholipid, cholesterol, and PEG-lipid) that encapsulates and protects the mRNA and mediates its cytosolic delivery.

2.1. The 5′ cap and untranslated regions

The 5′ cap, a 7-methylguanosine linked through a triphosphate bridge to the first nucleotide, is essential for efficient translation initiation and for protecting the transcript from exonucleolytic degradation. It has been importantly, a correctly formed cap (a Cap-1 structure bearing 2′-O-methylation) marks RNA as "self," preventing recognition by cytosolic sensors that would otherwise flag an uncapped or Cap-0 transcript as foreign [67]. The flanking UTRs are non-coding but functionally decisive: the 5′ UTR governs ribosome recruitment and scanning, while the 3′ UTR influences transcript half-life. Sequences derived from highly expressed genes—such as the human α- and β-globin 3′ UTRs, are frequently used, and high-throughput and machine-learning approaches are increasingly employed to identify UTR variants that maximise protein output.

2.2. The open reading frame and codon optimisation

The ORF encodes the antigen. Its sequence is optimised without altering the encoded protein by exploiting the redundancy of the genetic code—codon optimisation replaces

rare codons with synonymous, more frequently used ones to improve translational efficiency, and the guanine-cytosine content is often enriched to enhance transcript stability. Beyond raw expression, antigen design is itself an immunological lever: stabilising a viral surface protein in its prefusion conformation can increase immunogenicity by an order of magnitude, as demonstrated for the SARS-CoV-2 spike and the respiratory syncytial virus fusion protein [12]. For therapeutic cancer vaccines, the ORF instead encodes tumour-associated antigens or, in personalised products, patient-specific neoantigens derived from somatic mutations [13, 14].

2.3. Nucleoside modification: taming immunogenicity

Perhaps the single most consequential design choice is nucleoside modification. Unmodified uridine-containing mRNA is a strong agonist of innate RNA sensors, triggering a type I interferon response that both causes reactogenicity and paradoxically suppresses translation of the encoded antigen [3]. The substitution of uridine with N1-methylpseudouridine (m1Ψ) markedly reduces this innate recognition, increases the stability and translational capacity of the transcript, and underlies the two approved COVID-19 vaccines [4]. Importantly, this change does not remove immunogenicity, it re-tunes it to reduce excessive innate activation but retain the vigorous adaptive response required for protection. Thus, the degree of modification is a tunable parameter and for prophylactic vaccines it is desirable to minimize interferon-driven reactogenicity whereas for some cancer applications, a stronger, unmodified-mRNA-driven interferon signal could boost anti-tumour immunity.

2.4. Non-replicating versus self-amplifying mRNA

There are two main types. Conventional non-replicating mRNA (the format of the approved COVID-19 vaccines) produces antigen proportional to the number of transcripts delivered, and so a relatively high dose may be needed to generate a robust response. Self-amplifying RNA (saRNA) however adds the replicase machinery of an alphavirus, an RNA-dependent RNA polymerase, to the antigen ORF . The saRNA replicates within the cytoplasm to give rise to a much higher amount of antigen from a much lower dose and a longer duration of expression [16, 60, 68]. Because saRNA does not encode the viral structural proteins required to assemble infectious particles, it cannot replicate from cell to cell, and because it does not have a DNA intermediate there is no risk of genomic integration. The trade-off is that the double-stranded replication intermediates generated during amplification are themselves potent innate immune stimuli, which can limit expression; balancing this is an active area of saRNA engineering. In either form, the entire platform is manufactured by a cell-free enzymatic reaction, providing a flexibility and speed of manufacturing that cannot be matched by cell-based vaccine technologies [2].

2.5. Manufacturing: the cell-free production pipeline

One of the platform's main benefits is in the way the transcript is made. mRNA is generated by in vitro transcription, which is a cell-free enzymatic reaction where a bacteriophage RNA polymerase transcribes a DNA template encoding the antigen. The mRNA is then capped, purified and formulated in LNPs [2, 32]. The process is completely sequence-independent, since no live cells, eggs or cultures of pathogens are involved. To switch from one antigen to another, or to update an existing vaccine to match a drifted viral variant, all that needs to be changed

is the DNA template, with every downstream step, reagent and piece of equipment remaining the same. That's why the platform is known for its speed and is appropriate for a single, standard manufacturing plant that supports many products. An important quality control measure is the removal of double-stranded RNA by-products generated during transcription, as dsRNA is one of the most potent agonists of the innate sensors discussed below, and purification (e.g. chromatographic methods) directly improves both the translational yield and the tolerability of the final product [4, 5]. The field is still refining the manufacturing scalability, raw material supply and reproducibility of LNP encapsulation, which are non-trivial engineering problems.

3. Delivery Systems: The Lipid Nanoparticle

Naked mRNA is quickly broken down by common ribonucleases and, because of its large, anionic nature, is unable to cross the hydrophobic plasma membrane on its own. The lipid nanoparticle is the delivery system that rendered the platform clinically viable [17]. Modern LNPs are a four component formulation and each component has a specific role. • Ionizable lipid: the core functional of the particle. It is near-neutral at physiological pH, which makes it better tolerated and circulates well, but it becomes positively charged at the acidic environment of the endosome. This pH-dependent charge switch enables complexation with the RNA during formulation and, importantly, enables endosomal membrane destabilization and escape of the cargo into the cytosol – the rate limiting step of delivery. • Phospholipid (helper lipid): provides structural support to the lipid bilayer and helps membrane fusion. • Cholesterol: regulates membrane fluidity and particle stability, affecting intracellular trafficking. • PEGylated lipid: coats the particle surface, controls particle size, prevents aggregation and prolongs circulation time.

LNPs are taken up by the cell through cell-mediated endocytosis . The ionizable lipid releases the mRNA into the cytoplasm where it is translated by the host ribosomal machinery. The particle also determines biodistribution. Intramuscular injection, the standard route, results in expression predominantly at the site of injection and in the draining lymph nodes, which are home to professional antigen-presenting cells - an anatomically favorable outcome for vaccination [5]. The LNP is now known to play an active immunological role beyond delivery. Empty particles lacking RNA are also immunostimulatory, with the ionizable lipid component signaling through Toll-like receptor 4 to activate the transcription factors NF-κB and IRF as well as engaging the NLRP3 inflammasome in monocytes. This intrinsic adjuvant activity, discussed below, is a defining and somewhat serendipitous feature of the platform.

4. Innate Immune Sensing and Activation

The innate immune system is the first responder to an mRNA vaccine and the signals it generates dictate the quality and magnitude of the adaptive response that follows. An immune system did not evolve to differentiate a therapeutic transcript from a viral genome; both are foreign RNA introduced into a cell, and both are patrolled by an

array of pattern recognition receptors (PRRs) that sense RNA based on its location, structure, and chemical composition [5].

4.1. Pattern recognition receptors

This is centered around two families of sensors. Endosomal Toll-like receptors, TLR3, TLR7 and TLR8, sense RNA within the endocytic compartment, with TLR3 recognizing double-stranded RNA (dsRNA) and TLR7 and TLR8 detecting guanosine- and uridine-rich single-stranded RNA. A parallel layer of surveillance is provided by the cytosolic RIG-I-like receptors RIG-I and MDA5. RIG-I preferentially binds short dsRNA molecules with a 5′-triphosphate, whereas MDA5 recognizes long dsRNA and polymerizes into filaments on the dsRNA. The TLR pathways and the RIG-I and MDA5 pathways, which signal through the mitochondrial adaptor MAVS after ligand binding, share the downstream event of activation of the transcription factors IRF3, IRF7 and NF-κB. Two other cytosolic sensors are also activated by dsRNA and inhibit protein synthesis directly. The protein kinase R (PKR) phosphorylates the translation initiation factor eIF2α and thereby blocks translation, whereas the 2′-5′-oligoadenylate synthetase (OAS)/RNase L system degrades cellular and viral RNA. Table 1 summarizes the main sensors and their outputs.

Table 1. Innate RNA sensors relevant to mRNA vaccines and their downstream effects.

Sensor	Location	Ligand recognised	Principal downstream output
TLR3	Endosome	Double-stranded RNA	TRIF → IRF3 → type I IFN; NF-κB
TLR7 / TLR8	Endosome	GU-rich single-stranded RNA	MyD88 → IRF7 / NF-κB; IFN-α, pro-inflammatory cytokines
RIG-I	Cytosol	Short 5′-triphosphate dsRNA	MAVS → IRF3 / NF-κB → type I IFN
MDA5	Cytosol	Long double-stranded RNA	MAVS → type I IFN; drives $CD8^+$ T-cell priming
PKR	Cytosol	Double-stranded RNA	eIF2α phosphorylation → translational arrest
OAS / RNase L	Cytosol	Double-stranded RNA	RNA degradation; limits antigen expression
TLR4 / NLRP3	Surface / cytosol	Ionizable lipid of the LNP	NF-κB / IRF; IL-6, IL-1β – intrinsic adjuvant effect

4.2. The type I interferon response: a double-edged sword

The shared endpoint of TLR and RIG-I-like receptor activation is the production of type I interferons (IFN-α and IFN-β). Secreted interferon acts in an autocrine and paracrine fashion through the IFN-α/β receptor (IFNAR), triggering the JAK–STAT cascade and the transcription of hundreds of interferon-stimulated genes that collectively establish an antiviral state. In the context of vaccination this response is genuinely double-edged. On one hand, type I interferon is a powerful natural adjuvant: it promotes dendritic cell maturation, enhances antigen cross-presentation, and supports the priming of antigen-specific $CD8^+$ T cells. In contrast, an interferon response that is too much or too early is counterproductive, because the translation of

the antigen that the vaccine is supposed to express is shut down by PKR- and OAS-mediated pathways, and because systemic interferon contributes to the fever, malaise, and inflammation at the injection site that are experienced as reactogenicity. The art of mRNA vaccine design is to thread this needle, producing enough innate stimulation to license a robust adaptive response but not so much as to suppress antigen production or cause intolerable side effects.

4.3 Nucleoside modification and the resolution of the paradox

Nucleoside modification is the principal tool for resolving this paradox. By incorporating m1Ψ, the transcript largely escapes recognition by the RNA sensors that would trigger a translation-suppressing interferon response, allowing sustained antigen expression [3, 4]. This explains an apparent contradiction: the approved COVID-19 vaccines use modified mRNA specifically to reduce innate RNA sensing, yet they remain highly immunogenic. The reason is that a substantial part of their adjuvanticity is supplied not by the RNA but by the LNP carrier.

4.4 The lipid nanoparticle as an intrinsic adjuvant

Studies dissecting the mechanism of adjuvanticity have shown that the LNP is a critical driver of the innate response. In the draining lymph node, LNPs activate innate immune cells and elicit the production of interleukin-6 (IL-6), a cytokine essential for the induction of T follicular helper cells and germinal centre B cells—the machinery of high-affinity antibody production [7]. Where the mRNA is unmodified and the LNP contains particular ionizable lipids, the RNA is sensed by TLR7 and TLR8 while the lipid engages the NLRP3 inflammasome in monocytes, and the interleukin-1 family cytokines IL-1β and its antagonist IL-1ra emerge as key regulators of the resulting inflammation, with notable differences between species [8, 9]. The practical implication is that the immunogenicity of an mRNA vaccine is the integrated output of two adjuvant systems—the RNA and its carrier—whose relative contributions can be independently engineered.

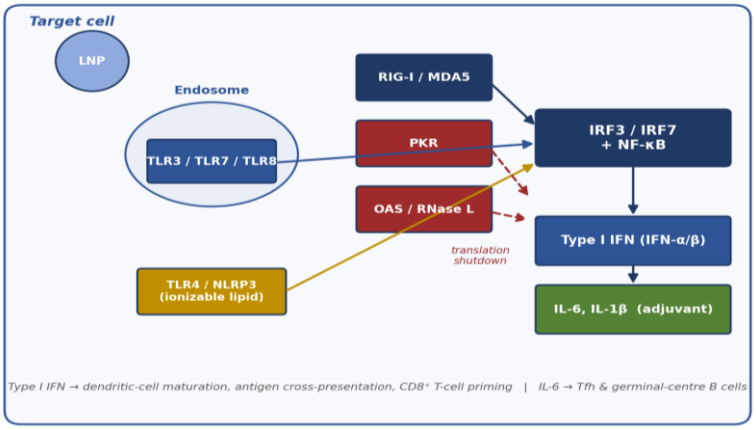


Fig. 2. Innate immune sensing of mRNA vaccines. Endosomal Toll-like receptors (TLR3/7/8) and cytosolic RIG-I-like receptors (RIG-I, MDA5) detect the RNA, while PKR and the OAS/RNase L system restrict translation (dashed red). The ionizable lipid of the carrier signals through TLR4 and the NLRP3 inflammasome. These pathways converge on IRF3/7 and NF-κB, driving type I interferon and adjuvant cytokines (IL-6, IL-1β) that instruct the ensuing adaptive response.

5. Bridging Innate and Adaptive Immunity: Antigen Presentation

The innate response is valuable primarily because it instructs the adaptive one. Dendritic cells (DCs) are the essential intermediaries. Following vaccination, DCs at the injection site and in the draining lymph node take up LNPs and translate the encoded antigen, or acquire antigen released by neighbouring transfected cells such as myocytes. The innate signals described above—type I interferon, IL-6, and inflammasome-derived cytokines—drive DC maturation, upregulating MHC molecules and the co-stimulatory ligands CD80 and CD86 and prompting migration to the T-cell zones of the lymph node [5].

Because the antigen is synthesised inside the cell, it gains natural access to both arms of the presentation machinery. Endogenously translated protein is processed by the proteasome and loaded onto MHC class I molecules for surveillance by $CD8^+$ T cells, while protein routed through the endolysosomal pathway is presented on MHC class II to $CD4^+$ T cells. In addition, DCs can cross-present exogenously acquired antigen on MHC class I, a process strongly favoured by the type I interferon milieu that mRNA vaccines create. This dual and cross-presentation is a mechanistic advantage of the platform over conventional protein subunit vaccines, which are largely confined to the MHC class II pathway and therefore elicit weaker cytotoxic responses. It is precisely this capacity to prime $CD8^+$ T cells that makes mRNA vaccines attractive not only against viruses but also as cancer immunotherapeutics, where tumour-cell killing depends on cytotoxic T lymphocytes [13, 14].

6. Modulation of the Adaptive Immune Response

The ultimate purpose of an mRNA vaccine is to generate a specific, potent, and durable adaptive response. The platform characteristically induces a well-balanced response encompassing both humoral and cellular immunity, together with the memory compartments that provide long-term protection.

6.1. Humoral immunity and the germinal centre

The generation of high-affinity, neutralising antibodies is the primary correlate of protection for most prophylactic vaccines, and it is orchestrated within the germinal centre. Antigen-specific B cells that encounter the vaccine antigen migrate to the border of the B-cell follicle, where they receive help from $CD4^+$ T follicular helper (Tfh) cells. As noted above, LNP-induced IL-6 is critical for the differentiation of these Tfh cells, and their availability is often the limiting factor in the quality of the antibody response [7, 53]. Within the germinal centre, B cells undergo iterative cycles of somatic hypermutation and affinity-based selection, progressively refining the affinity of their B-cell receptors. mRNA-LNP vaccines are notable for inducing exceptionally durable germinal centre reactions, which persist for weeks to months and yield high-affinity, class-switched antibodies together with long-lived plasma cells that secrete antibody from the bone marrow and memory B cells poised for rapid recall [8].

6.2. Cellular immunity

The cellular response is equally important and, in some applications, decisive. $CD4^+$ helper T cells provide the cytokine and co-stimulatory support that sustains both the humoral response and the $CD8^+$ compartment. mRNA-LNP vaccines characteristically polarise $CD4^+$ cells toward a T helper 1 (Th1) phenotype, marked by the production of interferon-γ, which favours antiviral and antitumour immunity and is considered a

desirable and reassuring safety profile, as Th2-skewed responses have historically been associated with vaccine-associated enhanced disease for certain pathogens [11, 12]. $CD8^+$ cytotoxic T lymphocytes, primed through the MHC class I and cross-presentation pathways described earlier, directly recognise and kill cells displaying the target antigen. Type I interferon signalling is an important driver of this $CD8^+$ priming, linking the innate sensing events at the start of the response to the cytotoxic effector cells at its conclusion.

6.3. Immunological memory

Durable protection depends on the establishment of memory. mRNA vaccines generate memory B cells and both central and effector memory T-cell populations, along with long-lived plasma cells. Upon re-exposure to the antigen, memory B cells differentiate rapidly into antibody-secreting cells and memory T cells mount an accelerated effector response, producing the anamnestic protection that is the goal of vaccination. The kinetics and durability of this memory—and the extent to which booster doses are required to maintain it—remain areas of active clinical investigation, particularly for rapidly evolving pathogens where antigenic drift can erode the neutralising capacity of pre-existing antibodies.

6.4. Correlates of protection and immunomonitoring

A key practical question is how to translate these immunological responses into a reliable measure of protection. Neutralizing antibody titres have become a strong correlate of protection against symptomatic COVID-19 infection for vaccines, offering a measurable benchmark against which to assess new formulations and boosters without the need to repeat large efficacy trials each time. But antibodies are only part of the story. T-cell responses are more difficult to measure at scale but appear more durable and more resistant to antigenic drift than neutralizing antibody and may account for the continued protection against severe disease as antibody-mediated protection against mild infection wanes. For therapeutic cancer vaccines the relevant correlates are different again; induction of neoantigen-specific T cells, their persistence and functional quality are the immunological readouts most closely linked to clinical benefit, and standardized assays for these responses are still maturing [14, 29]. Uncertainty over correlates has direct implications for vaccine development, timing of boosters and regulatory assessment, and motivates the deep immunophenotyping—germinal center sampling, single-cell profiling of responding lymphocytes and longitudinal cytokine measurement—that increasingly accompanies platform clinical trials. A more accurate map from measurable immune parameters to protection would allow for the rational, rather than empirical optimization of dose, schedule and antigen design.

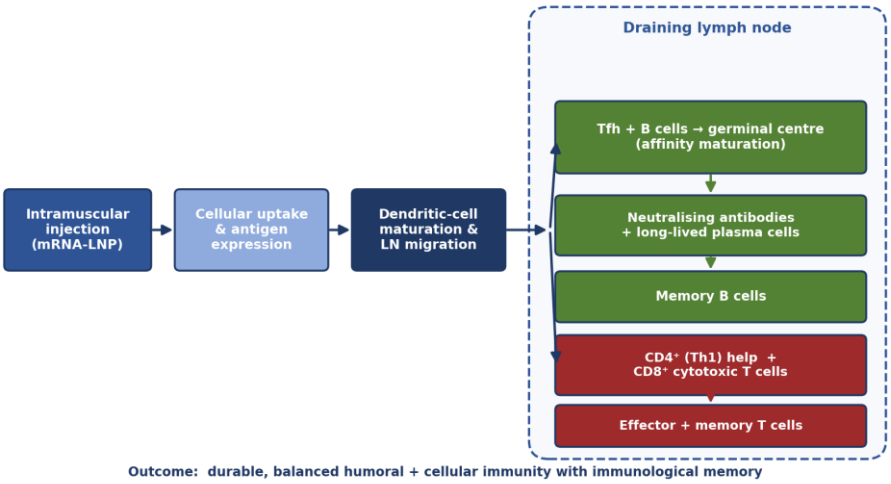


Fig. 3. From vaccination to adaptive immunity and memory. Following intramuscular injection, the mRNA-LNP is taken up and the antigen expressed; matured dendritic cells migrate to the draining lymph node, where the response branches into a humoral arm (T follicular helper and germinal-centre B cells producing neutralising antibodies, long-lived plasma cells, and memory B cells) and a cellular arm ($CD4^+$ Th1 help and $CD8^+$ cytotoxic T cells, yielding effector and memory populations).

7. Balancing Immunogenicity and Reactogenicity

The same intrinsic mechanisms that render mRNA vaccines immunogenic also render them reactogenic. The transient local and systemic symptoms that are frequently reported after vaccination, such as pain at the injection site, fatigue, headache, myalgia, and fever, are the clinical manifestations of the innate inflammatory cascade, mediated by type I interferon, IL-6, and IL-1 family cytokines released in response to both the RNA and the LNP [8, 9]. This results in an inherent design tension, as the very activation necessary to elicit a strong and durable adaptive response is the activation that underlies reactogenicity. Rational vaccine design, therefore, attempts to separate the two whenever possible.

There's a number of levers. Nucleoside modification reduces RNA-driven innate sensing and thus some reactogenicity while maintaining adaptive potency. Optimization of the ionizable lipid and overall LNP composition can alter the inflammatory profile, and dose reduction, especially feasible with self-amplifying formats, can reduce systemic exposure to inflammatory stimuli. Further unwanted innate activation is mitigated by purification of the IVT product to remove dsRNA contaminants, which are potent PRR agonists. The overarching goal is a vaccine that provides enough adjuvant signal to drive robust and long-lived immunity, but that remains well tolerated, and the growing mechanistic understanding of precisely which receptors and cytokines mediate each effect is what makes such targeted optimization increasingly feasible [5].

8. Applications in Disease

8.1. Infectious diseases

The prophylactic vaccines against COVID-19 remain the defining application of the platform. BNT162b2 and mRNA-1273 both encode a prefusion-stabilised SARS-CoV-2 spike protein and demonstrated approximately 95% efficacy against symptomatic infection in pivotal trials, eliciting strong neutralising antibody titres alongside Th1-skewed $CD4^+$ and $CD8^+$ T-cell responses [10, 11, 12]. The platform's speed enabled rapid updating of the antigen sequence to match emerging variants, illustrating a durable strategic advantage. Beyond SARS-CoV-2, mRNA vaccines are in clinical development against influenza, respiratory syncytial virus, and a range of other pathogens, and self-amplifying formats are being pursued to achieve equivalent immunity at lower doses and cost [16].

8.2. Cancer immunotherapy

The application in which the immunomodulatory reach of mRNA vaccines is most fully exploited is oncology. Therapeutic cancer vaccines aim to direct a cytotoxic T-cell response against tumour cells, and the platform's ability to prime $CD8^+$ T cells makes it particularly well suited to this task. The most advanced strategy is personalised neoantigen vaccination: a patient's tumour and healthy tissue are sequenced, tumour-specific mutations are identified computationally, the neoantigens most likely to be immunogenic are selected, and an individualised mRNA vaccine encoding them is manufactured [13]. Because neoantigens arise from somatic mutations absent in normal tissue, they can be targeted with minimal risk of autoimmunity.

Clinical results have been encouraging. In resected high-risk melanoma, the personalised vaccine mRNA-4157 (V940) combined with the checkpoint inhibitor pembrolizumab improved recurrence-free survival relative to pembrolizumab alone in a randomised phase 2b trial, and phase 3 evaluation is under way [15]. In resected pancreatic ductal adenocarcinoma—a notoriously immune-refractory malignancy—the individualised vaccine autogene cevumeran induced neoantigen-specific T-cell responses in a subset of patients, and those immunological responders showed delayed disease recurrence, with vaccine-induced T cells detectable years after treatment [14]. Off-the-shelf products targeting shared tumour antigens, such as BNT111 in melanoma, are also in development. A recurring theme is synergy with immune checkpoint inhibitors: the vaccine supplies tumour-specific T cells, while checkpoint blockade removes the brakes that the tumour microenvironment imposes on them. Representative products and their immunological rationale are summarised in Table 2.

The immunological logic of these combinations merits emphasis. A therapeutic cancer vaccine on its own must overcome an established, immunosuppressive tumour microenvironment that can render newly primed T cells anergic or exhausted. By pairing the vaccine with checkpoint inhibitors—which block inhibitory receptors such as PD-1 or its ligand PD-L1—the two modalities act on complementary points of the cancer-immunity cycle: the mRNA vaccine expands the pool of tumour-specific T cells, while checkpoint blockade preserves their function within the tumour. This division of labour is why the most striking clinical signals to date have emerged from

combination regimens rather than vaccine monotherapy. It also creates a natural role for molecular diagnostics: serial monitoring of circulating tumour DNA can detect minimal residual disease and identify the post-surgical window in which tumour burden is lowest and vaccination is most likely to succeed, tying the success of the therapeutic vaccine to the sensitivity of companion diagnostics.

Table 2. Representative approved and investigational mRNA vaccine products.

Product / candidate	Indication	Immunological principle & status
BNT162b2; mRNA-1273	COVID-19	Prefusion-stabilised spike; strong neutralising antibody + Th1/CD8 response. Approved.
mRNA-4157 (V940)	Resected high-risk melanoma	Personalised neoantigen vaccine + pembrolizumab; improved recurrence-free survival in phase 2b (KEYNOTE-942). Phase 3 ongoing.
Autogene cevumeran	Pancreatic ductal adenocarcinoma	Individualised neoantigen vaccine; durable neoantigen-specific T-cell responses correlate with delayed recurrence.
BNT111	Advanced melanoma	Off-the-shelf vaccine targeting four shared tumour antigens; activity in checkpoint-refractory disease.
saRNA candidates	Influenza, RSV, boosters	Self-amplifying constructs achieve durable antigen expression at markedly lower doses.

8.3. Synthesis of clinical evidence

Taken together, the clinical data validate the immunological principles outlined above across two very different therapeutic contexts. In the prophylactic setting, the two pivotal COVID-19 trials reported vaccine efficacy of approximately 95% for BNT162b2 and 94% for mRNA-1273 against symptomatic infection, an outcome underpinned by the strong neutralising antibody and Th1-biased T-cell responses the platform elicits [10,11] (Figure 4A). In the therapeutic setting, the randomised phase 2b KEYNOTE-942 trial of the personalised vaccine mRNA-4157 (V940) in combination with pembrolizumab reported an 18-month recurrence-free survival of 79%, compared with 62% for pembrolizumab alone (hazard ratio 0.56), in patients with resected high-risk melanoma [15] (Figure 4B). These figures illustrate a consistent theme: the magnitude and quality of clinical benefit track closely with the vaccine's capacity to generate the specific immune effectors—neutralising antibodies for viral protection, cytotoxic T cells for tumour control—that its design is intended to elicit.

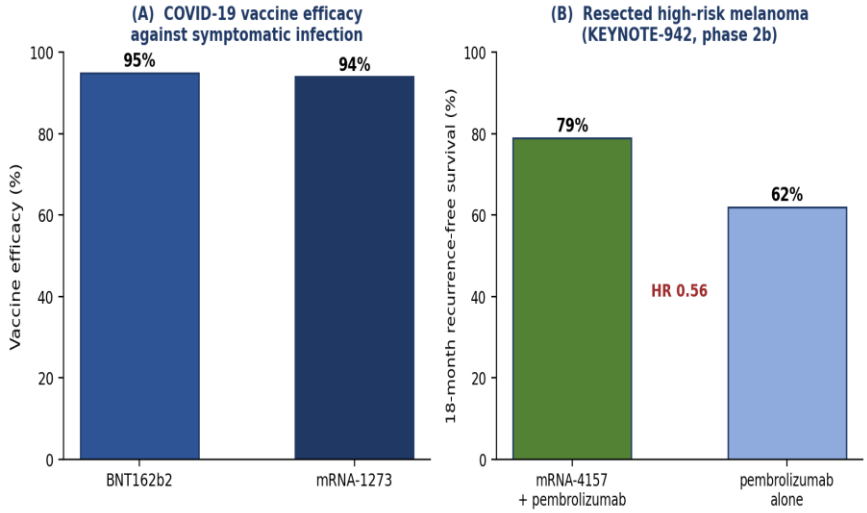


Fig. 4. Summary of key clinical results. (A) Vaccine efficacy against symptomatic COVID-19 for the two approved mRNA vaccines. (B) Eighteen-month recurrence-free survival in resected high-risk melanoma for the personalised neoantigen vaccine mRNA-4157 plus pembrolizumab versus pembrolizumab alone (KEYNOTE-942, phase 2b). Values are approximate and drawn from the respective pivotal reports [10,11,15].

9. Challenges and Future Directions

Despite its remarkable trajectory, the platform faces genuine limitations, and addressing them defines the current research agenda.

- **Stability and cold chain:** the inherent lability of RNA has historically demanded stringent frozen storage, complicating global distribution. Advances in formulation, lyophilisation, and thermostabilising excipients aim to relax these requirements and broaden access in resource-limited settings.
- **Targeted and extrahepatic delivery:** current LNPs distribute predominantly to the injection site, draining lymph nodes, and liver. Engineering particles that target specific cell types or tissues—for example, particular dendritic cell subsets—would sharpen immunogenicity and reduce off-target effects.
- **Self-amplifying RNA:** saRNA promises equivalent immunity at a fraction of the dose, but its double-stranded replication intermediates provoke innate responses that can curtail antigen expression; reconciling amplification with tolerability is a central engineering challenge [60,68].
- **Durability and variant coverage:** sustaining protective immunity against rapidly evolving pathogens without excessive boosting will require antigen designs that elicit broadly cross-reactive responses.
- **Tolerogenic mRNA vaccines:** the same platform can be inverted to suppress rather than activate immunity. By delivering an autoantigen in the absence of innate danger signals—using heavily modified, non-inflammatory mRNA—it is possible to induce antigen-specific tolerance, an approach being explored for autoimmune diseases and allergy.

More broadly, the maturation of neoantigen prediction algorithms, the integration of mRNA vaccines with other modalities such as checkpoint inhibitors and cell therapies, and the coupling of therapeutic vaccination to sensitive diagnostics for minimal residual disease all point toward an increasingly personalised and combinatorial future. The manufacturing agility of the platform means that lessons learned in one indication transfer rapidly to others, compressing development timelines across the entire field [18,19].

10. Conclusion

mRNA vaccines are a paradigm shift in immunology and vaccinology. Their unique mechanism - providing genetic instructions for the recipient's own cells to make and present the antigen - allows them to engage the immune system with a completeness few other platforms can match, orchestrating innate sensing, dendritic-cell-mediated presentation via both MHC pathways, germinal-centre-driven antibody maturation and cytotoxic T-cell immunity in one coordinated response. What makes the platform immunologically sophisticated is that nearly everything is tunable: transcript stability and expression, nucleoside composition to set innate activation, antigen design to steer the immune response, and the lipid nanoparticle itself that can be used as an intrinsic and tunable adjuvant.

The COVID-19 pandemic has shown beyond all doubt that this control can be translated into safe, effective and rapidly deployable products at global scale. The frontier now reaches far beyond infectious disease into personalized cancer immunotherapy, where the platform’s capacity to prime tumour-specific cytotoxic T cells is already delivering clinical benefits, and even into the intentional induction of immune tolerance. With delivery technologies, self-amplifying designs and antigen engineering strategies still maturing, mRNA vaccines are likely to become a versatile and long-lasting pillar of modern medicine, with a defining strength being the precision with which it can direct and modulate the immune response.

Conflict of interest **:** Authors are declared that there is no conflict of interest regarding this study.

Ethics approval **:** Not applicable

Code availability **:** Available from the author on reasonable request.

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Availability of data and materials **:**

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