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MRNA VACCINE TECHNOLOGIES BEYOND COVID-19: PROPHYLACTIC AND THERAPEUTIC APPLICATIONS

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ABSTRACT

The rapid development and global deployment of mRNA vaccines against SARS-CoV-2 transformed vaccinology and validated a platform with exceptional speed, adaptability, and potency. Beyond COVID-19, the same nucleoside-modified mRNA–lipid nanoparticle technology is now being applied to a broad range of infectious diseases and therapeutic indications. This review critically examines the current state and future potential of mRNA vaccine technologies beyond SARS-CoV-2, with a focus on prophylactic vaccines for influenza, respiratory syncytial virus, cytomegalovirus, Zika virus, HIV, and rabies, as well as therapeutic cancer vaccines and personalized neoantigen approaches. Key aspects of mRNA design—such as nucleoside modification, sequence optimization, and lipid nanoparticle formulation—are discussed in relation to immunogenicity, reactogenicity, and delivery. Clinical progress through 2022 is summarized, including multivalent influenza candidates and personalized cancer vaccines in combination with checkpoint inhibitors. Major challenges remain in optimizing delivery to non-hepatic tissues, reducing systemic reactogenicity, improving durability, and addressing manufacturing and storage limitations. Emerging strategies such as self-amplifying mRNA, circular RNA, and targeted lipid nanoparticles may further broaden the platform. Overall, mRNA vaccines are positioned to become a central pillar of preventive and therapeutic medicine, but translational hurdles must be addressed through continued multidisciplinary research.

Keywords: mRNA Vaccine; Lipid Nanoparticle; Infectious Disease; Cancer Immunotherapy; Self-Amplifying RNA; Personalized Neoantigen Vaccine

1 INTRODUCTION

The concept of using mRNA as a therapeutic or vaccine platform was proposed decades ago, but early efforts were hindered by instability, poor translation, and excessive innate immune activation. Three breakthroughs enabled clinical success: the incorporation of modified nucleosides to reduce Toll-like receptor recognition, improved mRNA purification and sequence optimization, and efficient delivery using lipid nanoparticles. The COVID-19 pandemic accelerated development, leading to the approval of two mRNA vaccines, BNT162b2 and mRNA-1273, which demonstrated high efficacy and an acceptable safety profile. These vaccines encode the SARS-CoV-2 spike protein and have been administered to billions of individuals worldwide.

The success against COVID-19 has generated intense interest in extending mRNA technology to other pathogens and diseases. Because mRNA vaccines are synthesized in vitro and encode only the antigen of interest, they avoid the need for pathogen culture and can be rapidly redesigned. This is particularly valuable for pandemic preparedness and for addressing pathogens with high antigenic variability. Beyond infectious diseases, mRNA is being evaluated as a therapeutic cancer vaccine, where the goal is to induce T-cell responses against patient-specific tumor neoantigens. Despite the promise, significant challenges remain, including delivery to specific cell types, durability of expression, and management of adverse events.

This review summarizes the state of mRNA vaccine technologies beyond COVID-19, with an emphasis on published literature and clinical developments through 2022. It covers platform design, prophylactic applications, therapeutic applications, and current limitations, and outlines future directions.

2 THE mRNA VACCINE PLATFORM: DESIGN AND MECHANISM

An mRNA vaccine is a synthetic single-stranded RNA molecule encoding an antigen. The basic structure includes a 5′ cap, a 5′ untranslated region, the coding sequence, a 3′ untranslated region, and a polyadenylated tail. These elements influence translation efficiency and stability. A key innovation was the use of modified nucleosides such as pseudouridine or N1-methylpseudouridine, which reduce recognition by pattern recognition receptors and increase protein expression while limiting type I interferon responses. Codon optimization and GC content adjustment further enhance translatability.

Delivery is primarily achieved by lipid nanoparticles composed of ionizable cationic lipids, cholesterol, helper phospholipids, and PEGylated lipids. Ionizable lipids are neutral at physiological pH but become positively charged in endosomes, facilitating membrane disruption and cytoplasmic release. After intramuscular injection, LNP-mRNA is taken up by local cells, including antigen-presenting cells, and the encoded protein is translated and presented via both MHC class I and class II pathways. This dual presentation supports CD8+ cytotoxic T-cell responses and CD4+ helper responses, while the innate immune activation induced by the LNP provides adjuvant effects.

The platform's versatility arises from the fact that any protein antigen can be encoded by simply altering the mRNA sequence. This enables multivalent vaccines, combination of conserved and variable antigens, and rapid response to emerging variants or novel pathogens.

3 PROPHYLACTIC APPLICATIONS BEYOND COVID-19

3.1 Influenza

Influenza vaccines have traditionally relied on egg- or cell-based production of hemagglutinin, requiring months of lead time and frequent mismatch with circulating strains. mRNA vaccines offer the possibility of rapid seasonal updates and universal influenza vaccines targeting conserved regions. Moderna's quadrivalent mRNA-1010 encodes hemagglutinin from four seasonal strains and entered phase 3 trials in 2022. Pfizer and BioNTech are also evaluating mRNA influenza candidates. A landmark preclinical study demonstrated that a multivalent nucleoside-modified mRNA vaccine encoding hemagglutinin from all 20 known influenza A and B subtypes induced broad protection in mice and ferrets. Although clinical translation remains to be validated, these findings support the potential for a universal influenza vaccine.

3.2 Respiratory Syncytial Virus

Respiratory syncytial virus is a major cause of lower respiratory tract infection in infants and older adults. The viral F protein exists in a metastable prefusion conformation that is the primary target of neutralizing antibodies. mRNA vaccines encoding a stabilized prefusion F protein have shown promising immunogenicity in early-phase trials. mRNA-1345, Moderna's RSV candidate, entered phase 3 trials in 2022. The platform allows inclusion of multiple F protein variants or combinations with other antigens.

3.3 Cytomegalovirus

Cytomegalovirus is a leading infectious cause of congenital disability and a significant problem in transplant recipients. Vaccine development has been challenging due to the virus's complex entry mechanisms and immune evasion. mRNA-1647 consists of six mRNAs encoding the CMV pentamer complex and glycoprotein B. Phase 2 data showed robust neutralizing antibody and T-cell responses in both seronegative and seropositive individuals. A phase 3 trial in women of childbearing age was initiated in 2021.

3.4 Zika Virus

Zika virus causes congenital neurologic abnormalities following maternal infection. No licensed vaccine exists. mRNA-1893 encodes the Zika virus prM-E protein, which forms virus-like particles. Phase 1 trials showed strong neutralizing antibody responses. The ability to generate virus-like particles from mRNA is particularly attractive for flavivirus vaccines, as it mimics native virion structure without replication.

3.5 HIV

HIV vaccine development has been hindered by extreme viral diversity and the need to induce broadly neutralizing antibodies. mRNA allows sequential or germline-targeting strategies, in which multiple mRNAs encoding different envelope proteins are administered to guide B-cell maturation. Preclinical studies have shown that mRNA encoding HIV envelope trimers can induce neutralizing antibodies in animal models. Several mRNA HIV vaccine candidates entered phase 1 trials in 2022, including those expressing engineered envelope trimers and mosaic immunogens.

3.6 Rabies and Other Pathogens

Rabies mRNA vaccines encoding the glycoprotein have demonstrated protective immune responses in animal models and early human studies. Additional targets include Epstein–Barr virus, Nipah virus, and malaria antigens. The flexibility of the mRNA platform enables rapid development of vaccines against emerging infectious diseases, as demonstrated by COVID-19.

4 THERAPEUTIC APPLICATIONS

4.1 Cancer Vaccines

Therapeutic cancer vaccines aim to generate or amplify tumor-specific T-cell responses. mRNA is well suited for this purpose because multiple patient-specific neoantigens can be encoded in a single construct. Somatic mutations in tumor cells generate neoantigens that are not present in normal tissue, providing potential targets for immune recognition.

Personalized mRNA cancer vaccines involve sequencing the patient's tumor, predicting immunogenic neoantigens, and manufacturing an mRNA vaccine encoding several selected neoepitopes. Early clinical trials demonstrated feasibility and induction of neoantigen-specific T cells. In 2022, Moderna and Merck reported that the personalized mRNA vaccine mRNA-4157/V940 in combination with pembrolizumab reduced the risk of recurrence or death compared with pembrolizumab alone in patients with high-risk resected melanoma. These results, although preliminary at the time, provided important proof of concept for the personalized approach.

Non-personalized off-the-shelf cancer vaccines target shared tumor antigens. BioNTech's BNT111 encodes four melanoma-associated antigens and has shown immune responses in phase 1/2 studies. Other candidates target HPV-associated malignancies, prostate cancer, and ovarian cancer. Combination with checkpoint inhibitors is a common strategy to overcome immunosuppression.

4.2 Intratumoral mRNA

Intratumoral delivery of mRNA encoding cytokines such as IL-12, IL-15, or costimulatory molecules can modulate the tumor microenvironment. Phase 1 trials have shown that intratumoral mRNA can induce local and systemic immune responses. This approach may complement systemic immunotherapy.

4.3 Therapeutic Vaccines for Chronic Infections

Therapeutic vaccination against chronic hepatitis B and human papillomavirus has been explored. mRNA encoding HBV antigens can stimulate T-cell responses in animal models. Clinical studies are ongoing, but evidence through 2022 was limited.

5 CHALLENGES AND CURRENT LIMITATIONS

5.1 Reactogenicity and Innate Immune Activation

Local and systemic adverse events, including pain, fever, fatigue, and headache, are common after mRNA vaccination. While generally transient, these effects may limit acceptability and dose escalation in therapeutic settings. Unmodified or poorly purified mRNA triggers stronger innate responses; optimized sequences and modified nucleosides reduce but do not eliminate reactogenicity.

5.2 Delivery and Biodistribution

Systemically administered LNP-mRNA accumulates primarily in the liver, which is a major limitation for therapeutic applications beyond hepatic targets. Intramuscular injection restricts expression largely to local tissue and draining lymph nodes, which is acceptable for vaccines but not for protein replacement. Targeted delivery to lungs, spleen, or solid tumors requires novel formulations and targeting ligands.

5.3 Durability of Expression and Immunogenicity

mRNA expression is transient, typically peaking within 24–48 hours and lasting a few days. This may be insufficient for some therapeutic indications requiring sustained protein levels. While transient expression reduces the risk of genomic integration, it necessitates repeated dosing for chronic diseases. Strategies such as self-amplifying mRNA and circular RNA are being developed to extend expression.

5.4 Manufacturing and Storage

Although mRNA can be rapidly synthesized, manufacturing at scale requires specialized equipment and raw materials. The cold-chain requirements of LNP-mRNA vaccines, particularly at ultra-low temperatures for early COVID-19 vaccines, pose logistical challenges in resource-limited settings. Lyophilization and thermostable formulations are under investigation.

5.5 Regulatory and Immunological Considerations

The novelty of the platform requires continued pharmacovigilance. Rare adverse events such as myocarditis observed after COVID-19 mRNA vaccination require mechanistic understanding and risk stratification. For therapeutic cancer vaccines, patient-specific manufacturing creates regulatory and quality-control challenges.

6 FUTURE PERSPECTIVES

Several innovations are likely to shape the next generation of mRNA technologies. Self-amplifying mRNA, which contains RNA-dependent RNA polymerase sequences, allows amplification of the antigen-encoding RNA within the cell, potentially reducing dose and extending expression. Circular RNA, lacking free ends, may exhibit increased stability and reduced innate immune activation. Improved ionizable lipids and targeting ligands may enable organ-specific delivery beyond the liver. Combination vaccines encoding multiple antigens from different pathogens could improve immunization coverage.

In oncology, the integration of personalized mRNA vaccines with immune checkpoint inhibitors and other immunotherapies is a major focus. The positive signals from melanoma trials are expected to be confirmed in larger studies. mRNA-based in vivo delivery of monoclonal antibodies and cytokines may expand therapeutic applications. In infectious diseases, universal influenza and multivalent combination vaccines are realistic near-term goals.

Pandemic preparedness will be enhanced by mRNA platform libraries and rapid manufacturing capabilities. Global initiatives to establish regional manufacturing capacity and thermostable formulations will improve equitable access. Continued research into mechanisms of innate immune activation and adverse events will guide optimization.

7 CONCLUSION

mRNA vaccines have moved beyond COVID-19 and are now being evaluated for a wide array of infectious diseases and therapeutic applications. The platform's flexibility, speed, and ability to induce both humoral and cellular immunity make it uniquely suited to address unmet medical needs. Prophylactic candidates for influenza, RSV, CMV, Zika, HIV, and other pathogens are progressing through clinical development, while therapeutic cancer vaccines have shown encouraging efficacy when combined with checkpoint blockade. Despite significant challenges related to delivery, durability, reactogenicity, and manufacturing, ongoing innovations in self-amplifying RNA, circular RNA, and targeted lipid nanoparticles promise to overcome many of these limitations. The mRNA platform is likely to become a foundational technology in medicine, with implications extending far beyond its initial success against COVID-19.

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