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Priyanka Malakar

Assistant Professor,
 Department of Veterinary
 Physiology and Biochemistry,
 College of Veterinary and
 Animal Science Navania,
 Udaipur, Rajasthan, India

Kanchan Singh

Project Associate-I, Division
 of Pharmacology, CSIR-Indian
 Institute of Integrative
 Medicine, Jammu, Jammu and
 Kashmir, India

Ghanshyam Sahu

Ph.D Scholar, Division of
 Biochemistry, ICAR IVRI,
 Izatnagar, Bareilly, Uttar
 Pradesh, India

mRNA therapeutics beyond vaccines: Emerging applications, challenges, and future perspectives

Priyanka Malakar¹, Kanchan Singh², Ghanshyam Sahu³

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ABSTRACT

Messenger RNA (mRNA) technology has emerged as an important platform in modern medicine, particularly following the successful development of mRNA-based vaccines against COVID-19. However, the potential of mRNA extends well beyond vaccination. Because mRNA can transiently instruct cells to produce a desired protein without requiring genomic integration, it can be investigated as a therapeutic platform for protein replacement, cancer immunotherapy, genome editing, regenerative medicine, and immune-cell engineering (Chien *et al.*, 2026; Pardi *et al.*, 2018; Qin *et al.*, 2022; Verbeke *et al.*, 2019) [1, 2, 3, 4]. Advances in nucleoside modification, sequence optimization, purification, and lipid nanoparticle (LNP) delivery have significantly improved the stability, translation, and therapeutic potential of mRNA (Karikó *et al.*, 2005; Karikó *et al.*, 2008; Hou *et al.*, 2021; Reichmuth *et al.*, 2016) [5, 6, 7, 8]. Current research is investigating mRNA-based approaches for rare metabolic disorders, cancer, genome editing, and other diseases (Chien *et al.*, 2026; Parhiz *et al.*, 2024) [1, 9]. Nevertheless, challenges involving extrahepatic delivery, transient expression, immunogenicity, dose control, manufacturing, and long-term safety remain important barriers (Chien *et al.*, 2026; Hou *et al.*, 2021; Wang *et al.*, 2026) [1, 7, 10]. This review discusses the fundamental principles of mRNA therapeutics, major applications beyond vaccines, delivery technologies, current challenges, and future prospects for next-generation mRNA medicines.

Keywords: MRNA therapeutics, Messenger RNA, Lipid nanoparticles, Protein replacement, Cancer immunotherapy, Gene editing, CRISPR, RNA delivery, Precision medicine

1. Introduction

Messenger RNA is a single-stranded RNA molecule that transfers genetic information from DNA to ribosomes, where it serves as a template for protein synthesis. The concept of using mRNA as a therapeutic molecule has existed for several decades, but early development was limited by poor stability, inefficient cellular delivery, rapid degradation, and unwanted activation of the innate immune system (Pardi *et al.*, 2018; Qin *et al.*, 2022) [2, 3].

A major breakthrough occurred when researchers demonstrated that chemical modification of RNA nucleosides could reduce unwanted immune recognition and improve protein production. Karikó and colleagues demonstrated that incorporation of pseudouridine could substantially reduce inflammatory responses while increasing translational activity, establishing an important foundation for modern therapeutic mRNA technology (Karikó *et al.*, 2005; Karikó *et al.*, 2008) [5, 6].

The COVID-19 pandemic subsequently demonstrated that mRNA could be rapidly designed, manufactured, and administered on a large scale. However, vaccination represents only one application of the technology. Unlike DNA-based gene therapy, mRNA generally functions in the cytoplasm and does not need to integrate into the genome. Its temporary expression therefore provides an opportunity to produce therapeutic proteins without permanently altering the patient's genetic material (Chien *et al.*, 2026; Qin *et al.*, 2022; Pardi *et al.*, 2018) [1, 3, 11].

Recent research has increasingly moved toward what has been described as "mRNA therapeutics 2.0." This emerging phase includes enzyme replacement, cancer immunotherapy, genome modification, immune-cell engineering, and other therapeutic applications (Chien *et al.*, 2026) [1]. Consequently, mRNA is increasingly being considered a versatile drug platform rather than simply a vaccine technology.

2. Structure and basic principles of mRNA therapeutics

Therapeutic mRNA is designed to efficiently produce a specific protein inside target cells. A typical synthetic mRNA contains a 5' cap, 5' untranslated region, coding sequence, 3' untranslated region, and poly(A) tail. These structural components influence RNA stability, intracellular persistence, and translation efficiency (Qin *et al.*, 2022; Xu *et al.*, 2020) [3, 12].

Corresponding Author: Priyanka Malakar

Assistant Professor,
 Department of Veterinary
 Physiology and
 Biochemistry, College of
 Veterinary and Animal
 Science Navania, Udaipur,
 Rajasthan, India

One of the major advances in mRNA technology has been the incorporation of modified nucleosides. Modification of RNA nucleosides can decrease activation of innate immune receptors and improve protein production. The pioneering work of Karikó *et al.* demonstrated that pseudouridine-containing mRNA could produce higher protein expression with reduced inflammatory signaling (Karikó *et al.*, 2005; Karikó *et al.*, 2008) [5, 6].

Other strategies include codon optimization, optimization of untranslated regions, and modification of the poly(A) tail. These approaches can improve translation efficiency and increase the functional lifetime of therapeutic mRNA (Qin *et al.*, 2022; Xu *et al.*, 2020) [3, 12].

However, naked mRNA is highly susceptible to enzymatic degradation and has difficulty crossing cellular membranes. Therefore, an effective delivery system is generally required. Lipid nanoparticles have become one of the most clinically advanced technologies for mRNA delivery because they can protect RNA from degradation, facilitate cellular uptake, and promote release of RNA into the cytoplasm (Hou *et al.*, 2021; Reichmuth *et al.*, 2016; Schoenmaker *et al.*, 2021) [7, 8, 13].

3. Protein replacement therapy

One of the most promising applications of mRNA technology is protein replacement therapy. Many inherited diseases are caused by mutations that result in absent, deficient, or dysfunctional proteins. Conventional protein replacement may require repeated administration of recombinant proteins and may have limitations related to protein stability, distribution, and manufacturing (Chien *et al.*, 2026; Parhiz *et al.*, 2024) [1, 9].

mRNA provides an alternative strategy by delivering temporary instructions to cells so that they produce the required therapeutic protein themselves. This approach has attracted particular interest for rare metabolic diseases and other disorders involving protein deficiencies (Chien *et al.*, 2026; Parhiz *et al.*, 2024) [1, 9].

The temporary nature of mRNA expression can be advantageous because it avoids permanent genomic modification. However, the same characteristic also creates a limitation: because mRNA and the resulting proteins are eventually degraded, repeated administration may be required for chronic diseases (Chien *et al.*, 2026; Wang *et al.*, 2026) [1, 10].

Recent clinical development has therefore focused on improving the duration, consistency, and tissue distribution of therapeutic protein expression. These developments represent an important transition from experimental mRNA research toward clinically applicable protein-replacement therapies (Chien *et al.*, 2026; Parhiz *et al.*, 2024) [1, 9].

4. Cancer immunotherapy

Cancer is one of the most actively investigated applications of therapeutic mRNA. mRNA can be engineered to encode tumor-associated antigens, tumor-specific neoantigens, cytokines, antibodies, or immune-cell receptors (Zhang *et al.*, 2025; Yao, 2024; Biomarker Research, 2024; Fu *et al.*, 2025) [14, 15, 16, 17].

4.1 Personalized cancer vaccines

Tumor cells frequently contain genetic mutations that produce abnormal proteins known as neoantigens. These antigens can potentially be recognized by the patient's immune system. mRNA technology can encode multiple tumor-associated or patient-specific antigens in a single therapeutic formulation (Zhang *et al.*, 2025; Yao, 2024) [14, 15].

Personalized mRNA cancer vaccines can therefore be designed according to the molecular characteristics of an individual patient's tumor. In a typical approach, tumor sequencing is used to identify candidate mutations, bioinformatic methods are used to predict immunogenic neoantigens, and an mRNA formulation is subsequently designed to encode selected targets (Yao, 2024; Biomarker Research, 2024) [15, 16].

This strategy represents an important application of precision medicine. Instead of using the same antigen combination for every

patient, the vaccine can potentially be tailored to the unique molecular characteristics of an individual's tumor (Yao, 2024; Biomarker Research, 2024) [15, 16].

Recent research has investigated mRNA cancer vaccines in melanoma and other solid tumors. Although many approaches remain under clinical investigation, increasing evidence suggests that mRNA can serve as a flexible platform for personalized cancer immunotherapy (Zhang *et al.*, 2025; Yao, 2024; Biomarker Research, 2024; Fu *et al.*, 2025) [14, 15, 16, 17].

4.2 mRNA and immune-cell engineering

mRNA can also be used to temporarily modify immune cells. For example, mRNA can encode chimeric antigen receptors (CARs), allowing immune cells to recognize specific tumor-associated antigens. It can also encode cytokines and other immune-regulating proteins (Chien *et al.*, 2026; Zhang *et al.*, 2025) [1, 14].

An important advantage of mRNA-based cellular engineering is that expression is transient. Permanent genetic modification may create long-term safety concerns, whereas transient mRNA expression can provide greater control over the duration of cellular activity (Chien *et al.*, 2026) [1].

Recent research has also explored the possibility of delivering mRNA directly into the body to reprogram immune cells in vivo. Such approaches could potentially reduce the complexity and cost associated with conventional ex vivo cell therapies (Chien *et al.*, 2026; Zhang *et al.*, 2025) [1, 14].

5. mRNA-based genome editing

Another rapidly developing application is the use of mRNA to deliver genome-editing components. CRISPR-based systems can modify specific DNA sequences, and mRNA can be used to encode the nuclease component responsible for genome editing (Chien *et al.*, 2026; Molecular Therapy, 2025) [1, 18].

In a CRISPR-based approach, mRNA may encode a Cas protein while a guide RNA directs the editing machinery toward a selected genomic sequence. The transient expression of the Cas protein can be advantageous because prolonged expression of genome-editing machinery may increase the opportunity for unwanted editing events (Molecular Therapy, 2025) [18].

mRNA-based delivery has therefore been investigated as a means of providing temporary expression of genome-editing components. Potential applications include inherited disorders in which correction of a disease-causing mutation could provide therapeutic benefit (Chien *et al.*, 2026; Molecular Therapy, 2025) [1, 18].

However, genome editing introduces additional safety considerations. These include unintended genomic modifications, inefficient editing, immune responses against editing components, and difficulties achieving efficient delivery to the appropriate cells (Chien *et al.*, 2026; Molecular Therapy, 2025) [1, 18].

Consequently, successful mRNA-based genome editing will require improvements not only in editing efficiency but also in delivery specificity and control.

6. Regenerative medicine

mRNA technology may also contribute to regenerative medicine. Instead of permanently introducing genes into cells, mRNA can provide temporary instructions for producing growth factors, transcription factors, or other proteins involved in tissue repair and regeneration (Chien *et al.*, 2026; Qin *et al.*, 2022) [1, 3].

Researchers have investigated mRNA encoding proteins capable of influencing cell differentiation, proliferation, survival, angiogenesis, and tissue regeneration. The temporary nature of mRNA expression can be beneficial because biological signals can be delivered for a limited period without permanent genetic modification.

Potential applications include cardiovascular repair, tissue engineering, bone regeneration, and other regenerative strategies. However, efficient delivery to the desired tissue and precise control of the dura

tion and level of protein expression remain important challenges (Chien *et al.*, 2026; Verbeke *et al.*, 2019) [1, 4].

7. mRNA delivery technologies

The therapeutic potential of mRNA depends strongly on the ability to deliver it efficiently to the appropriate cells. Because RNA is large, negatively charged, and vulnerable to degradation, delivery is a major technological challenge (Hou *et al.*, 2021; Reichmuth *et al.*, 2016) [7, 8].

7.1 Lipid nanoparticles

Lipid nanoparticles are currently one of the most advanced delivery systems for mRNA. They protect RNA from degradation and facilitate cellular uptake and endosomal escape (Hou *et al.*, 2021; Reichmuth *et al.*, 2016) [7, 8].

LNPs generally contain ionizable lipids, helper lipids, cholesterol, and polyethylene glycol-associated lipids. The specific composition and physicochemical properties of these components influence particle stability, cellular uptake, biodistribution, and RNA release (Hou *et al.*, 2021; Reichmuth *et al.*, 2016; Schoenmaker *et al.*, 2021) [7, 8, 13].

The success of LNP-mRNA vaccines has demonstrated the clinical feasibility of this delivery platform. However, conventional LNPs tend to accumulate strongly in the liver after systemic administration, which limits their usefulness for diseases affecting other organs (Chien *et al.*, 2026; Hou *et al.*, 2021) [1, 7].

7.2 Targeted delivery

An important goal of current research is the development of tissue- and cell-specific delivery systems. Researchers are investigating changes in lipid composition, targeting ligands, peptides, polymers, and biomimetic systems to improve delivery to specific organs and cell populations (Hou *et al.*, 2021; Vasileva *et al.*, 2024; Wang *et al.*, 2024; Current Opinion in Chemical Biology, 2024) [7, 19, 20, 21].

Selective delivery could potentially improve therapeutic efficacy while reducing unwanted exposure to healthy tissues. For example, targeted nanoparticles could be designed to deliver mRNA preferentially to tumors, immune cells, muscle, or other organs (Chien *et al.*, 2026; Vasileva *et al.*, 2024) [1, 19].

Recent research emphasizes that the next generation of mRNA therapeutics will require delivery systems capable of overcoming physiological barriers and directing RNA to specific intracellular compartments (Vasileva *et al.*, 2024; Wang *et al.*, 2024; Current Opinion in Chemical Biology, 2024) [19, 20, 21].

8. Major challenges

Despite rapid progress, several challenges continue to limit the broader clinical application of mRNA therapeutics.

8.1 Stability

RNA is inherently susceptible to degradation. Although modified nucleosides, sequence optimization, and improved formulations have substantially increased stability, maintaining RNA integrity during manufacturing, storage, administration, and intracellular delivery remains important (Qin *et al.*, 2022; Hou *et al.*, 2021; Xu *et al.*, 2020) [3, 7, 12].

8.2 Transient expression

Transient expression is both an advantage and a limitation. It avoids permanent genetic modification but may require repeated administration for chronic diseases (Chien *et al.*, 2026; Parhiz *et al.*, 2024) [1, 9]. Researchers are therefore investigating approaches such as self-amplifying RNA and other next-generation RNA architectures that may increase protein production while reducing the amount of RNA required (Chien *et al.*, 2026; Karwa *et al.*, 2026) [1, 22].

8.3 Immunogenicity

RNA can activate innate immune receptors. Excessive immune activation may reduce therapeutic effectiveness and potentially cause adverse effects. Chemical modification, purification, and optimization

of RNA sequences have helped reduce unwanted immune stimulation (Karikó *et al.*, 2005; Karikó *et al.*, 2008) [5, 6].

Nevertheless, immunogenicity remains an important issue, particularly when repeated administration is necessary (Chien *et al.*, 2026; Wang *et al.*, 2026) [1, 10].

8.4 Delivery specificity

Efficient delivery to organs outside the liver remains one of the greatest challenges in mRNA therapeutics. A therapeutic mRNA may demonstrate excellent activity in laboratory experiments but have limited clinical effectiveness if it cannot reach the appropriate cells in sufficient quantities (Chien *et al.*, 2026; Hou *et al.*, 2021; Vasileva *et al.*, 2024) [1, 7, 19].

8.5 Dose control

The amount and duration of protein production must be carefully controlled. Excessive protein expression may cause undesirable biological effects, whereas insufficient expression may result in inadequate therapeutic activity. Dose optimization is therefore a major consideration in clinical development (Chien *et al.*, 2026; Wang *et al.*, 2026) [1, 10].

8.6 Manufacturing and scalability

Although mRNA can be manufactured relatively rapidly compared with some conventional biological products, production requires strict control of RNA integrity, purity, potency, and formulation quality (Hou *et al.*, 2021; Wang *et al.*, 2026) [7, 10].

Large-scale production also requires reproducible nanoparticle manufacturing and rigorous quality control. Improvements in manufacturing technology will therefore be important for making future mRNA therapies commercially and clinically accessible (Wang *et al.*, 2026) [10].

9. Future perspectives

The future of mRNA therapeutics is likely to involve increasingly sophisticated RNA molecules and delivery technologies. Researchers are investigating self-amplifying RNA, circular RNA, improved chemical modifications, targeted nanoparticles, and other RNA architectures (Chien *et al.*, 2026; Karwa *et al.*, 2026; Liu *et al.*, 2026) [1, 22, 23].

Self-amplifying RNA is particularly interesting because it contains elements that allow intracellular amplification of the RNA template. This may permit strong protein expression from lower doses than conventional non-amplifying mRNA (Karwa *et al.*, 2026) [22].

Another important direction is precision mRNA medicine. Instead of developing a single formulation for a broad patient population, therapies may increasingly be designed according to individual genetic or molecular characteristics. Personalized cancer vaccines represent one important example of this approach (Yao, 2024; Biomarker Research, 2024) [15, 16].

The combination of mRNA technology with genome editing, cell therapy, and nanotechnology may create therapeutic systems capable of temporarily reprogramming cells without permanently changing their genetic identity (Chien *et al.*, 2026) [1].

The development of improved delivery systems is likely to be particularly important. Current research is moving beyond conventional liver-targeting LNPs toward formulations capable of delivering mRNA to specific tissues and cell populations (Vasileva *et al.*, 2024; Wang *et al.*, 2024; Current Opinion in Chemical Biology, 2024) [19, 20, 21].

10. Conclusion

mRNA technology has developed from an experimental molecular biology concept into a clinically validated therapeutic platform. Although its most prominent application has been vaccination, mRNA has considerable potential in protein replacement therapy, cancer immunotherapy, genome editing, regenerative medicine, and im

mune-cell engineering (Chien *et al.*, 2026; Pardi *et al.*, 2018; Qin *et al.*, 2022; Verbeke *et al.*, 2019) [1, 2, 3, 4].

The major advantages of mRNA include transient protein expression, lack of genomic integration, flexible sequence design, and the ability to use a common manufacturing platform for different therapeutic proteins (Chien *et al.*, 2026; Qin *et al.*, 2022) [1, 3]. At the same time, limitations involving stability, delivery, immunogenicity, repeated administration, dose control, and manufacturing continue to restrict broader clinical applications (Hou *et al.*, 2021; Wang *et al.*, 2026) [7, 10].

The field is now moving toward "mRNA therapeutics 2.0," in which mRNA is being developed as a programmable medicine capable of temporarily instructing cells to produce therapeutic proteins, modify immune responses, and facilitate genome engineering (Chien *et al.*, 2026) [1]. Continued advances in RNA chemistry, nanoparticle engineering, tissue-specific delivery, and precision medicine could establish mRNA as an important therapeutic platform beyond vaccines.

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