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mRNA Therapeutics in Non-small Cell Lung Cancer (NSCLC)

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Abstract. The treatment of non-small cell lung cancer had remained the top cause of death globally, is one important area in oncology where messenger RNA therapy has shown promise. In contrast with traditional treatments, mRNA therapeutics offer quick development times and the ability to trigger immune responses without integrating into the host cell. mRNA therapeutics relies on the delivery of mRNA molecules into host cells then the intracellular production of these proteins subsequently activates adaptive immune responses, enabling targeted recognition and elimination of cancer cells. However, most of existing versions show tropism toward the liver, which reduces their effectiveness in targeting lung tissue, making delivery remains a major obstacle. To increase tissue preference and therapeutic accuracy, local delivery options are being actively investigated. Attention must also be taken to safety factors including the potential for unexpected protein translation including outcomes from repeated doses. Widespread clinical use is further hampered by cold-chain coordination, large-scale production, and strict regulatory requirements, especially in areas with limited resources. Personalized mRNA cancer vaccines are designed to eliminate immune responses against neoantigens that are specific to an individual's tumor. Self-amplifying RNA (saRNA), also known as self-replicating RNA (srRNA), represent a modified mRNA molecule that can replicate itself within host cells, enhancing protein expression and boosting the immune response. In addition, its extended and enhanced expression in vivo enables effective vaccination even at low doses.

Keywords: delivery system, immunotherapy, safety, challenges, personalized vaccines

1. Introduction

In recent years, mRNA technology has emerged as an important biomedical platform, gaining attention for its breakthrough in vaccine research and development. This progress demonstrates its high capacity for rapid developments, as well as its potential for cost-effective manufacturing and safe delivery [1].

Currently, NSCLC account for approximately 85% of the cases and remains the dominant subtype of lung cancer tend to be below 20% in most countries [2]. Most advanced NSCLC cases eventually develop resistance, highlighting an urgent need for novel therapeutic strategies. Molecular targeted therapies and immunotherapies have significantly improved the prognosis of

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NSCLC. However, the vast majority of advanced NSCLC develop resistance to current therapies and eventually progress.

Apart from these advances, it is essential to highlight the broader importance of the mRNA platform in the modern therapeutics. The mRNA treatment has the potential to overcome many limitations of conventional vaccines and therapeutics, including the fast-paced development and the ability to encode multiple antigens [3]. Since the mechanism of action occurs in the cytoplasm of the cells, mRNA-based treatment avoids the concerns of genomic disruption. The high-productive synthesis technology of mRNA in vitro also ensures the purity and consistency under strict restrictions, which ensures drug safety and efficacy.

Despite these advantages, several critical barriers remain that limit the full realization of mRNA therapeutics in oncology applications. Although lipid nanoparticles (LNPs) is the mainstream delivery method, but the targeting efficiency for tissues beyond the liver, such as lung tumors is still a challenge. The natural tropism of lipid nanoparticles to hepatocytes remains a major hurdle for targeting tissues such as the lungs [4].

Moreover, repeated administration of lipid nanoparticles (LNPs) can elicit the innate immune reactions, which may negatively impact both the safety and therapeutic performance of mRNA-based treatments. These challenges highlight the urgent necessity of developing advanced next-generation delivery systems with enhanced tissue specificity, especially for effective targeting of lung cancer.

mRNA represents a transformative therapeutic platform with the potential for safe and versatile applications. Although it provides clear advantages than traditional vaccines, several obstacles remain, most obviously the efficient delivery to tissues except hepatic one and the modulation of immune responses. Addressing these barriers through the rational design of advanced delivery systems will be crucial to release the full potential of mRNA therapeutics . Ongoing innovations in this field are expected to broaden the clinical use of mRNA-based strategies, with non-small cell lung cancer (NSCLC) standing out as a key focus for especially next-generation delivery technologies. Particularly, NSCLC represents an important place in next-generation mRNA delivery system.

2. Mechanism of mRNA treatment on NSCLC

The process of making mRNA vaccine begins with designing and synthesizing optimized mRNA molecules that code the targeted protein. This involves codon optimization based on tRNA abundance, modification of the untranslated regions to enhance stability and translation, and the addition of protective elements to prevent exonuclease degradation. Such protective elements include a 5’ cap to block 5’ exonucleases and promote ribosome recognition, a 3’ poly(A) tail to prevent 3’ exonuclease attack, chemically modified nucleotides to reduce nuclease recognition and immune activation, and secondary structures such as stem-loops that further stabilize the mRNA molecule.

The incorporation of pseudouridine into mRNA generates a non-immunogenic vector with enhanced translational efficiency and biological stability, since it avoids recognition by innate immune sensors, thereby preventing inflammatory cytokine release and sustaining effective protein synthesis [5]. To protect mRNA from enzymatic degradation and ensure efficient cellular uptake, the molecules are commonly encapsulated within lipid nanoparticles (LNPs). This encapsulation protects the transcript and promotes delivery into the cytoplasm through endocytosis process.

Once inside the cytoplasm, the mRNA directs the host cell’s translational machinery to produce the encoded protein. The synthesized protein can then be secreted into the cell surface to elicit

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adaptive immune responses. Therefore, mRNA-based therapeutics represent a novel drug modality that heavily influences the body's own protein synthesis system to generate therapeutic proteins in situ and enables applications in both vaccination field and protein replacement therapy [6].

Following the translation process, both the mRNA and its encoded protein undergo degradation through natural metabolic pathways, thereby minimizing risks of long-term accumulation. A key safety feature lies in the fact that mRNA functions solely in the cytoplasm without integrating into the host genome, eliminating the possibility of insertional mutagenesis that could disrupt normal gene function. The transient expression profile further ensures precise temporal regulation of protein production while reducing potential adverse effects.

Specifically, in the context of non-small cell lung cancer (NSCLC), mRNA therapeutics is a flexible approach to overcome challenges such as tumor heterogeneity, immune evasion, and therapeutic resistance. Ongoing early-phase clinical trials are investigating personalized neoantigen vaccines and combination strategies with immune checkpoint inhibitors (ICIs), with encouraging preliminary outcomes in terms of efficacy and safety, suggesting the potential ability to reshape therapeutic examples for advanced NSCLC.

mRNA vaccines have demonstrated a preliminary efficacy in NSCLC clinically. A study of multi-antigen mRNA vaccine CV9201 in stage III NSCLC patients was analyzed, that T-cell responses against at least one tumour-associated antigen were detected in 63% of 30 patients with a median progression-free survival of 5.0 months and overall survival of 10.8 months, and a 2-year survival rate of 26.7%. CV9202, is an improved next-generation version of CV9201, both of which are mRNA-based cancer vaccines developed for NSCLC, induced antigen-specific immunity in 21 (84%) of 25 patients with partial responses in some cases and stable disease in 48% [7].

However, NSCLC presents unique challenges compared with other mRNA therapeutic applications. Antigen selection in NSCLC must account for tumor heterogeneity, patient-specific neoantigens, and immune escape mechanisms, whereas infectious disease vaccines often target conserved pathogen proteins. Moreover, therapeutic goals differ: NSCLC mRNA therapies aim to treat established tumors and prevent recurrence, often in combination with ICIs, whereas infectious disease mRNA vaccines are primarily prophylactic. Finally, delivery strategies may be optimized to target tumor-draining lymph nodes and enhance local antigen presentation, a consideration less critical in vaccines for systemic infections.

3. Delivery system innovation

Currently, the delivery system with some drawbacks should be innovated into several aspects. Inhalation of nanomedicine formulations enables direct delivery of therapeutic agents to the lungs, allowing for higher local drug concentration at tumor sites and reduced systemic toxicity [8]. Therefore, local delivery via inhalation is a suitable alternative to deliver higher local drug concentration to the specific target side.

In addition, Stimuli-responsive nanocarriers can exploit the peculiar characteristics of the tumor microenvironment, such as acidic pH, enzymatic activity or redox potential, to trigger site-specific and controlled drug release; Compared to conventional systems for siRNA delivery, this type of platform can respond to local stimuli that are characteristics of the pathological area of interest, allowing the release of nucleic acids at the desired site [9]. Nanoparticle drug delivery system (NDDS) offers targeted delivery, microenvironment responsiveness, and site-specific release, enabling precise control over drug action.

Moreover, by harnessing their unique properties, exosomes are poised to revolutionize the diagnosis and treatment of NSCLC, offering a promising treatment method for more personalized

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and effective therapies.

Finally, Antibody–drug conjugates (ADCs) have emerged as a novel class of targeted cancer therapeutics, combining the specificity of antibodies with the cytotoxic potential of chemotherapeutic agents [10] .

These conjugates consist of monoclonal antibodies linked to cytotoxic drugs, which allow targeted delivery of the chemotherapy to send to tumor cells directly. Investigators in the phase 2 DESTINY-Lung01 trial observed an objective response rate (ORR) of 55%, median progression-free survival (PFS) of 8.2 months, and median overall survival (OS) of 17.8 months [11]. These promising results proof the potential of ADCs in treating HER2-mutated NSCLC, offering a targeted therapeutic option.

These advancements illustrate how newly-developed delivery system are innovating the NSCLC therapy by improving tumor targeting while reduce the systematic toxicity. Enhancing the therapeutic precision is a highlight of the system in a more efficient and personalized lung cancer treatment.

4. Safety considerations

Safety considerations are linked to the delivery system that adapted for treatment in NSCLC. LNP with positive charge are capable of disrupting cell membrane, inducing cytotoxicity. Also, the mRNA molecules can trigger immune responses due to pH-dependent or permanent cationic properties of the delivery systems, potentially leading to safety concerns, such as disruption of cellular membranes and organelles, release of degrading enzymes from lysosomes, and DNA damage. Besides, the cell distribution of LNPs in the tumor cell population varies. Injection into the tumor mass does not mean that mRNA expression in cancer cells, which may lead to safety issues for some therapies associating with direct cytotoxic effects.

In the immune response aspect, although mRNA vaccines are well-performed in treating - tolerated, some harmful events do occur. In a study of BNT116 combined with cemiplimab in patients with advanced NSCLC who could not receive platinum - based chemotherapy, all patients experienced treatment - related adverse events, with 15% related to the vaccine, including supraventricular tachycardia, hypoxia, and hypertension [12].

Moreover, there are concerns about the misinterpretation of modified mRNA sequences by cellular machinery, which may cause unintended immune responses. The cellular machinery that reads mRNAs slips when confronted with repeats of a chemical modification commonly found in mRNA therapeutics, leading to the production of off-target proteins and triggering a mechanical immune response.

When ribosomes encounter runs of N1-methylpseudouridine, they slip about 10% of the time, producing off-target proteins. In research of 21 individuals vaccinated with the Pfizer mRNA vaccine, about one-third exhibited unintended immune responses, though no adverse effects were observed. Importantly, the researchers demonstrated that by redesigning mRNA to eliminate these problematic possibilities, it can suppress off-target protein production while maintaining the intended protein output [13].

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5. Discussion

5.1. Regulatory and manufacturing challenges

The development of mRNA-based therapeutics for NSCLC presents regulatory and manufacturing challenges in many aspects, with the procurement and the quality control of raw materials. These materials must be sourced with consistent high quality to ensure safety and efficacy. Achieving batch-to-batch consistency for such critical components is both technically demanding and tightly regulatory, particularly under cGMP (current Good Manufacturing Practice) requirements.

During assessment, regulatory agencies require full characterization of mRNA sequence integrity, lipid formulation stability, and immunogenicity risk, with documentation demonstrating that the mRNA drug product has acceptable potency, purity, and safety profiles [14]. Preclinical models must predictive, and clinical-scale assays validated under GLP (Good Laboratory Practice), creating a high bar for data completeness and reproducibility. The transportation of mRNA therapies introduces additional complexity: these molecules are inherently unstable and often require ultra-cold chain coordination (for example, storage at −80 °C), prompting regulators to insist that transport conditions are strictly monitored to maintain product integrity.

From a manufacturing perspective, the cost of ultra-cold chain coordination and quality-controlled raw materials increases complexity and raises price for broad usage. Overcoming these challenges will require innovation in formulation— moving toward more thermostable lipid systems —and harmonization of regulatory expectations across jurisdictions to minimize redundant assessments.

Therefore, advancing mRNA drugs for NSCLC requires rigorous raw-material policies, strict assessment, and validated transportation systems—all reinforced by regulatory coherence and technological innovation.

5.2. Future directions

Future directions of using mRNA therapy in NSCLC are evolving in terms of new forms, with important advancement in new forms of the technology. One promising innovation is self-amplifying RNA (saRNA), which extends protein expression with fewer doses, therefore, potentially reducing toxicity. In addition, saRNA extends expression kinetics, resulting in higher total amount of protein produced while comparing to conventional mRNA [13].

Another new approach involves personalized mRNA vaccines designed to encode tumor-specific neoantigens derived from sequencing data on DNA, offering higher precision in targeting the mutational profile of each patient's cancer tumor. Similarly, refinements in lipid nanoparticle engineering and organ targeted delivery platforms developed to tackle one of the greatest limitations in current mRNA therapeutics-achieving effective targeting the lung tissue. These kind of new forms of mRNA therapeutics provide more expanding tools for NSCLC patients.

Clinical research is also showing significant breakthrough. In a meta-analysis across 32 clinical trials involving advanced solid tumors, mRNA vaccines showed a combined objective response rate (ORR) of 10.0% and a disease control rate (DCR) of 34.6%, with 1-year progression-free survival (PFS) at 38.4%, 2-year PFS at 20.0%, 1-year overall survival (OS) at 75.3%, and 2-year OS at 45.5% respectively, associated with the minimal high-grade adverse events (1.0%), overall providing a convincing safety and foundation [15].

Furthermore, the personalized mRNA vaccine BNT116, evaluated in advanced NSCLC patients in combination with docetaxel, achieved an ORR of 35% and disease control rate of 85%, with high

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safety and evidence of robust T-cell responses [16]. mRNA vaccines are also being evaluated in combination with immune checkpoint inhibitors to amplify antitumor immunity and delay resistance, reflecting a trend toward integrated therapeutic approaches. Such advances point toward a paradigm shift in how NSCLC may be treated soon.

Nevertheless, the moral issues should also be considered when publishing new mRNA technologies. The opportunities of getting access to mRNA therapies, particularly personalized vaccines that rely on high-throughput sequencing and bioinformatics, which raises questions of global equity, as only resource-rich nations may initially afford widespread use. Safety remains another critical issue: repeated administrations of lipid nanoparticle–based formulations have been shown to activate the innate immune responses, potentially limits efficacy of treatment or pose risks of inflammatory toxicity deeper.

6. Conclusion

The versatility of mRNA platforms enables rapid adaptation to resistance mechanisms, which allows for the design of treatments that can address the dynamic and complex nature of lung cancer. Evidence from preclinical and early clinical studies supports their ability to generate antigen-specific immune responses and enhance the efficacy of existing treatments. These findings reinforce that mRNA-based interventions may become integral components of future oncological practice.

Despite these advances, significant obstacles remain before widespread clinical application can be also shown. Targeted delivery is one of the most crucial issues, as current lipid nanoparticle systems preferentially accumulate in the liver rather than lung tissue, limiting therapeutic effectiveness in NSCLC. Moreover, the safety profile of mRNA therapeutics, while encouraging, requires continuous refinement. Unintended immune activation, production of off-target proteins, and variability in delivery efficiency all highlight the necessity for ongoing optimization in molecular design and formulation.

Manufacturing and regulatory hurdles present further challenges. The requirement for high-quality raw materials, stringent quality control under cGMP conditions, and ultra-cold storage significantly, which increase both the complexity and cost of production. Harmonizing regulatory frameworks across jurisdictions and developing thermostable formulations will be essential for ensuring global accessibility. Ethical considerations further emphasize the importance of addressing disparities in healthcare resources.

Looking forward, self-amplifying RNA technologies may reduce dosing frequency while sustaining protein expression, thereby improving safety and cost-effectiveness. Personalized vaccines based on patient-specific neoantigens are anticipated to provide unprecedented precision in targeting NSCLC, while continued innovation in nanoparticle engineering could finally resolve the issue of lung-specific delivery. As clinical data accumulate, combined therapies integrating mRNA vaccines with targeted drugs may emerge as standard practice, optimizing therapeutic outcomes and delaying resistance.

In conclusion, the rapid evolution of mRNA therapeutics underscores their transformative potential for NSCLC treatment. Through sustained innovation, clinical validation, and global collaboration, mRNA-based approaches are expected to move beyond experimental stages and into widespread clinical use in treating NSCLC.

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