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mRNA Beyond Vaccines: Encoding Therapeutic Proteins for Inhaled Lung Disease Treatment

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Introduction

Messenger RNA (mRNA) has emerged as a transformative therapeutic modality, revolutionizing the field of medicine by enabling the in situ production of proteins within target cells. While mRNA-based vaccines have dominated headlines due to their pivotal role in combating the COVID-19 pandemic, their potential extends far beyond infectious disease immunization. One of the most promising frontiers is the use of mRNA to encode therapeutic proteins for the treatment of chronic and acute lung diseases via inhaled delivery [1].

Lung diseases, including Cystic Fibrosis (CF), Alpha-1 Antitrypsin Deficiency (AATD), pulmonary fibrosis, asthma and Chronic Obstructive Pulmonary Disease (COPD), often result from the deficiency or dysfunction of specific proteins. Delivering mRNA directly to the lungs allows for localized protein expression, minimizing systemic exposure and enhancing therapeutic specificity. Inhaled mRNA delivery offers a non-invasive, direct route to target pulmonary tissues, which are otherwise challenging to reach through systemic administration. This explores the scientific basis, current progress, technical considerations and clinical potential of inhaled mRNA therapeutics for lung diseases, shifting the paradigm of respiratory medicine [2].

Description

The lungs present a unique opportunity and challenge for mRNA-based therapeutics. They are highly vascularized, provide a vast absorptive surface area and are readily accessible via inhalation. Importantly, many lung diseases are localized, allowing for direct therapeutic targeting. Enables high protein concentrations at the site of pathology. Minimizes off-target effects and systemic toxicity. Inhalation is patient-friendly and avoids the complications associated with injections. Facilitates quick protein expression in acute disease settings. Therapeutic mRNAs can be designed to encode a wide array of proteins. Successful mRNA therapy hinges on the careful engineering of the mRNA molecule to ensure stability, efficient translation and reduced immunogenicity. 5' capping and 3' polyadenylation enhance translation efficiency and stability. Optimization of 5' and 3' UTRs improves ribosomal recruitment and protein yield. Using codons preferred by human ribosomes enhances protein production. Incorporation of modified bases (e.g., pseudouridine) reduces innate immune activation and increases stability. Allows for lower doses by enabling intracellular replication and prolonged protein expression [3].

Lipid Nanoparticles (LNPs) are the most established vehicle for mRNA delivery. They protect mRNA from enzymatic degradation, facilitate cellular uptake and aid endosomal escape. Traverse the mucus barrier without getting trapped. Penetrate deep into the alveolar and bronchial epithelium.

Avoid triggering excessive immune responses. Withstand shear forces during aerosolization. Bind mRNA at low pH and release it in cells. Enhance membrane fusion. Stabilizes the lipid bilayer. Improve particle stability and distribution. Efficient delivery of inhaled mRNA depends not only on the formulation but also on the method of administration. Jet and mesh nebulizers convert liquid LNP-mRNA formulations into fine aerosols. Offer portability and stability, but formulation challenges remain. Require careful propellant and excipient selection to maintain LNP integrity. Particle size, aerodynamic behavior and deposition patterns must be tailored to reach specific lung regions. Deep lung delivery (1–5 μm range) is often ideal for alveolar targeting. A growing body of research supports the use of mRNA therapeutics for a variety of lung diseases. mRNA encoding functional CFTR protein has restored chloride transport in vitro and in animal models. Clinical trials (e.g., Translate Bio/Sanofi) have explored nebulized mRNA therapy in CF patients [4].

Immune activation is both a potential benefit and a liability of mRNA therapy. While vaccines exploit innate and adaptive immune responses, therapeutic protein expression aims to minimize them. Use of modified nucleosides (e.g., m1Ψ, 5mC). Optimized purification to remove double-stranded RNA contaminants. Tailored dosing and delivery to avoid overwhelming immune activation. Local lung inflammation, cytokine release and bronchospasm are potential adverse effects that must be closely monitored in clinical development. Production of inhalable mRNA therapeutics must meet stringent quality and safety standards. Rigorous purification to remove impurities and contaminants. Formulation stability under storage and aerosolization conditions. GMP-compliant manufacturing pipelines for clinical use. Advances in microfluidics, automated formulation platforms and lyophilization are facilitating the large-scale production of pulmonary mRNA therapies. While the regulatory pathway for injectable mRNA vaccines has been established, inhaled mRNA presents unique challenges. Demonstrating local efficacy and safety in the respiratory tract. Developing standardized assays for lung-specific biomarkers. Addressing variability in patient inhalation patterns and lung function. Ensuring long-term safety with repeated administration. Engagement with regulatory bodies, early phase trials and patient-centric design will be essential for clinical translation. Ligand-functionalized LNPs for cell-specific targeting (e.g., alveolar type II cells). Co-delivery of mRNA with small molecules or gene-editing tools (e.g., CRISPR). Enhanced safety profiles and environmental sustainability [5].

Conclusion

mRNA-based therapeutics represent a new era in the treatment of lung diseases, extending far beyond their initial application in vaccines. By encoding therapeutic proteins and delivering them directly to the lungs, mRNA therapies offer a targeted, efficient and flexible platform for managing a wide spectrum of respiratory conditions. With continued innovation in mRNA design, nanoparticle delivery, inhalation technology and clinical science, the vision of treating genetic, inflammatory and neoplastic lung diseases through inhaled mRNA is becoming an achievable reality. Bridging the gap between laboratory promise and clinical impact will require multidisciplinary collaboration, patient engagement and robust translational research. As the field evolves, inhaled mRNA therapeutics are poised to redefine the standards of respiratory care and personalized medicine.

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Conflict of Interest

None.

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