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Review Paper

Inhaled Lipid Nanoparticles: A Transformative Pulmonary Delivery Platform for Cystic Fibrosis Therapy

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ABSTRACT

Cystic fibrosis (CF) is a debilitating autosomal recessive genetic disorder characterized by defective CFTR protein function, leading to viscous mucus accumulation, chronic pulmonary infections, and progressive lung damage.[2] Conventional oral or intravenous therapies for CFTR modulators (e.g., lumacaftor/ivacaftor) and antibiotics suffer from limited lung bioavailability, systemic toxicity, and poor patient adherence. Inhaled lipid nanoparticles (LNPs) represent an innovative drug delivery system that enables targeted pulmonary deposition, enhanced mucus penetration, sustained release, and reduced off-target effects.[24] This review comprehensively examines LNP classifications (liposomes, solid lipid nanoparticles [SLNs], nanostructured lipid carriers [NLCs], and hybrids), formulation strategies, physicochemical characterization, and aerosolization techniques. Preclinical evidence demonstrates LNPs restoring up to 55% CFTR chloride transport via mRNA delivery and eradicating pseudomonas aeruginosa biofilms with encapsulated antibiotics.[21] Clinical trials, including approved formulations like Arikayce® (liposomal amikacin), validate safety and efficacy. Challenges in scalability, mucus barriers, and regulatory approval are discussed alongside future directions in personalized, combination therapies. Inhaled LNPs hold transformative potential to improve CF outcomes and quality of life

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INTRODUCTION

Cystic fibrosis (CF) affects over 70,000 individuals worldwide, primarily Caucasians, with a median life expectancy of ~40 years despite CFTR modulator advancements. Mutations in the CFTR gene (>2,000 identified, F508del in ~50% of cases) impair chloride transport, dehydrating airway surface liquid (ASL) and promoting thick mucus, impaired mucociliary clearance, recurrent infections [1-3], inflammation, and complications like bronchiectasis and airflow obstruction.

Current therapies include oral CFTR correctors (lumacaftor) and potentiators (ivacaftor), which synergistically enhance chloride transport but are limited to tablet forms, resulting in suboptimal lung concentrations and systemic side effects. Targeted pulmonary drug delivery (TPDD) via inhalation circumvents first-pass metabolism, achieves high local drug levels, and minimizes toxicity.[4-7]

LNPs—biocompatible,

biodegradable carriers—excel in encapsulating hydrophobic/hydrophilic agents, nucleic acids, and proteins for sustained release.

This review synthesizes LNP mechanisms in CF, types, formulation/ characterization, preclinical/ clinical data (including pharmacokinetics/ biodistribution), marketed products, patents, and prospects, drawing from recent studies [29]

2. Pathophysiology of Cystic Fibrosis and Unmet Needs

CFTR mutations are classified into five classes: I (no synthesis), II (misfolding, e.g., F508del), III (gating defects), IV (conductance issues), and V (reduced synthesis).[21-22,28] Defective CFTR reduces ASL chloride secretion and heightens sodium absorption via ENaC, thickening mucus and fostering bacterial biofilms, oxidative stress, and inflammation.

Table 1: Classification of CFTR Mutation

| Class | Defect | Examples | Prevalence | Therapeutic Implications |
|-------|--|---------------|------------|--|
| I. | No protein synthesis (nonsense/ stop codons) | G542X, W1282X | ~10% | Gene therapy (mRNA, read-through agents) |
| II. | Misfolding/ trafficking defect | F508del | ~50% | Correctors(e.g., lumacaftor) |
| III. | Gating defect | G551D | ~4% | Potentiators (e.g., ivacaftor) |
| IV. | Conductance defect | R117H | ~3% | Potentiators |
| V. | Reduced synthesis | 3849+10kbC>T | ~3% | mRNA amplification |
| VI. | Reduced stability (expanded class) | Various | Variable | Stabilizers |

Daily treatment burdens include nebulized antibiotics, mucolytics (dornase alfa), and modulators, with infection risks, malnutrition, and high costs (~\$300,000/year for modulators). Unmet needs: curative gene therapies, affordable

options, and complication management. Inhaled LNPs address these by enabling direct lung delivery of modulators, antibiotics, siRNA (e.g., anti-ENaC), and mRNA

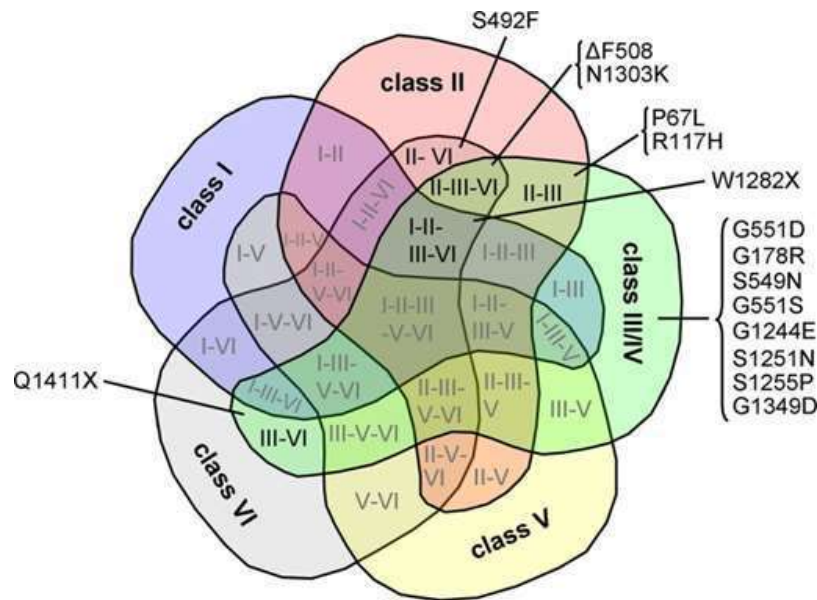


Figure 1: CFTR Mutation Classes Venn Diagram [32]

Venn diagram showing overlapping defects in major mutations (e.g., $\Delta F508$ as II-III-VI).

3. Lipid-Based Nanoparticles: Characteristics and Advantages

LNPs are vesicular systems self-assembled from amphiphilic lipids, encapsulating therapeutics in aqueous cores or bilayers. Key advantages in CF:

Targeted Lung Deposition: $<3 \mu\text{m}$ aerosols penetrate deep alveoli; mucus-penetrating designs (neutral zeta potential -10 to $+10$ mV) overcome barriers.

Drug Protection/Stability: Shield from enzymatic degradation; sustained release prolongs efficacy (e.g., amikacin SLNs reduce dosing frequency).

Reduced Toxicity: Localized delivery minimizes systemic exposure (e.g., nephrotoxicity from aminoglycosides).

Mucus Penetration: PEGylation or deformable liposomes (ethosomes/transfersomes) enhance diffusion.

Versatility: Encapsulate small molecules (ivacaftor), nucleic acids (CFTR mRNA), peptides.

Combination Therapy: Co-deliver modulators/antibiotics for synergy.

Biocompatibility: Low immunogenicity; GRAS lipids (DPPC, cholesterol).

Challenges: Limited loading for SLNs, gelation, drug leakage.

3.1 Types of LNPs

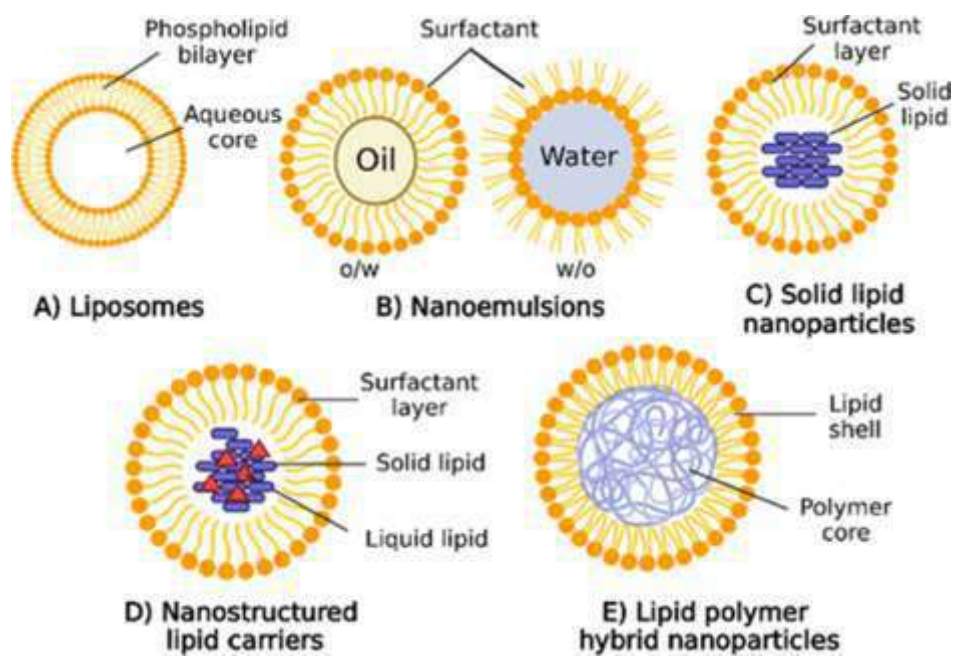


Figure 2: Schematic of LNP Types for Drug Delivery[33]

Illustration of liposomes, SLNs, NLCs, lipid nanoemulsions, and hybrid LNPs.

| Type | Structure | Size (nm) | Key Features | CF Applications |
|-------------------|--|-----------|---|--|
| Liposomes | Phospholipid bilayers | 80–300 | High EE (>99%); sustained release | Tobramycin, gentamicin, ciprofloxacin; biofilm penetration |
| SLNs | Solid lipid matrix | 10–1000 | Controlled release; biocompatibility | Amikacin, colistin; anti- <i>P. aeruginosa</i> |
| NLCs | Solid + liquid lipids | 100–400 | Higher loading; prevents expulsion | Tobramycin, ivacaftor/lumacaftor; mucus penetration |
| Hybrid NPs | Lipid-polymer (e.g., PLGA core + DPPC shell) | 100–150 | Muco-inertia; gene silencing | siRNA (anti-NFκB, ENaC); PNA for CFTR modulation |
| Others | Ethosomes, virosomes, archaeosomes, exosomes | 20–200 | Flexibility, stability, natural targeting | Baicalein (mucus-penetrative chitosan NPs); mRNA exosomes |

4. Formulation, Design, and Characterization

4.1 Manufacturing Techniques

Thin-Film Hydration: For liposomes (e.g., cefoperazone MLVs with DPPC:cholesterol 7:3).

Hot Homogenization/ Emulsification: SLNs/NLCs (e.g., amikacin SLNs at 70°C).

Solvent Injection: Nucleic acid LNPs (ionizable lipids + cmRNA).

Spray Drying: Lipid-coated microparticles for DPIs.

Cryoprotectants (mannitol/trehalose) ensure stability post-lyophilization.

Lipid selection: Phospholipids (DPPC/DSPC for rigidity), cholesterol (stability), surfactants

(Tween 80 for dispersion). Excipients: PEG for stealth, ligands for targeting.

4.2 Characterization

Size/Distribution: DLS, NTA (hydrodynamic radius); TEM/SEM/Cryo-TEM for morphology.

Zeta Potential: Electrophoretic light scattering (neutral for mucus penetration).

EE: UV/HPLC; >80–99% typical.

Stability: DSC for phase transitions; size/zeta over time.

Aerosol Performance: Next Generation Impactor (NGI); fine particle fraction >50% for deep lung.

Table 2: Key Formulation Parameters for Inhaled LNPs

| Parameter | Optimal Range | Impact on CF Delivery |
|------------------------|---------------|---|
| Particle Size | 100–300 nm | Enhances alveolar deposition; mucus penetration |
| Zeta Potential | -10 to +10 mV | Reduces electrostatic trapping in mucus |
| EE (%) | >80 | Maximizes drug payload for sustained release |
| Polydispersity Index | <0.3 | Ensures uniform aerosolization |
| pKa (Ionizable Lipids) | 6.5–7.6 | Promotes endosomal escape in lung epithelia |

5. Preclinical Efficacy, Pharmacokinetics, and Biodistribution

LNPs achieve high lung retention (>50% dose), prolonged release (up to 48–72 h), and uniform biodistribution.

Antibiotics: Liposomal amikacin reduces *P. aeruginosa* CFU by 2 logs; SLNs couple with lactose for alveolar uptake.

CFTR Modulators: PEG-NLCs with lumacaftor/ivacaftor restore ion transport in murine models; reduce fibrosis.

Nucleic Acids: LNP-cmCFTR (nasal) recovers 55% chloride efflux (14 days); siRNA hybrids silence ENaC 50% (1 week).

PK/BD: Nebulized NLCs show broad pulmonary distribution, minimal systemic spillover; exosomes enhance mRNA/protein delivery 2–3-fold vs. synthetic liposomes.

Table 3: Key Preclinical Studies (Expanded)

| Drug | LNP Type | Outcomes | PK/BD Highlights |
|--------------------------|------------|---|--------------------------------|
| Amikacin | Liposomes | 2-log CFU reduction; prolonged lung retention | >50% lung dose at 24 h |
| Ivacaftor/ Lumacaftor | PEG-NLC | Improved chloride transport; fibrosis reduction | 70% alveolar retention |
| CFTR mRNA | LNPs | 55% CFTR restoration (14 days) | Nasal: 55% efflux recovery |
| siNFκB | Hybrid NPs | Local anti-inflammatory; mucus penetration | 30–50% ENaC silencing (1 week) |

6. Clinical Trials and Marketed Formulations

Approved: Arikayce® (liposomal amikacin, 2018) for MAC infections in CF; reduces exacerbations.

Ongoing/Completed (Updated to 2025):

- **MRT5005 (CFTR mRNA LNPs):** Phase 1/2; stable FEV1 but hypersensitivity.

- **Ciprofloxacin DPI/Liposomal:** Phase III; well-tolerated, once-daily.
- **New:** BI 3720931 (inhaled lentiviral gene therapy, Phase 1, 2025); 9–15% CFTR expression in preclinical, multi-dose safe.[15]
- RCT2100 (ReCode mRNA LNP, Phase 1/2, FDA Orphan 2025); selective lung targeting.
- ARCT-032/VX-522 (Arcturus/Vertex mRNA LNPs, Phase 1/2 for CF/PCD); no completed inhaled LNP-mRNA trials yet.

Table 4: Clinical Summary (Updated 2025)

| Product | Drug | Status | Key Findings |
|------------|-----------------|---------------------|---|
| Arikayce® | Amikacin | Approved 2018 | Improved sputum eradication; reduced exacerbations |
| MRT5005 | CFTR mRNA | Phase 1/2 | No FEV1 benefit; safe but hypersensitivity |
| Pulmaquin | Ciprofloxacin | Discontinued (2016) | Effective but halted for commercial reasons |
| BI 3720931 | Lentiviral CFTR | Phase 1 (2025) | 9–15% epithelial CFTR expression; multi-dose feasible |
| RCT2100 | CFTR mRNA LNP | Phase 1/2 (2025) | Lung-selective; aerosol delivery in humans |
| ARCT-032 | CFTR mRNA LNP | Phase 1/2 | Ongoing for CF; enhanced stability via LOOP platform |

7. Patents and Intellectual Property

Key patents focus on nebulized mRNA (WO2020106946A1),[24] codon-optimized CFTR mRNA (US20180333457A1)[25], and LNP compositions (ES2865699T3) [29]. Recent 2025 filings emphasize SORT LNPs for CRISPR/CFTR editing (e.g., lung-specific homology-directed repair).

8. Challenges and Future Perspectives

Challenges: Mucus/size filtering, scalability, immunogenicity (PEG alternatives), regulatory (GMP aerosol stability).

Future:

Personalized LNPs: Genotype-specific (e.g., Class I mRNA).[13]

Smart Designs: pH-responsive for CF microenvironment; AI-optimized formulations.

Combinations: LNP + modulators + CRISPR (e.g., prime editing for W1282X).

Translation: Accelerate Phase III; cost-reduction via generics. Sequential trial participation to maximize opportunities.

CONCLUSION

Inhaled LNPs revolutionize CF management by enabling precise, sustained pulmonary delivery of diverse therapeutics. From preclinical CFTR restoration to approved antibiotics and emerging 2025 gene therapies, evidence underscores efficacy and safety. Overcoming barriers through innovation will integrate LNPs into standard care, extending survival and enhancing life quality for CF patients.

REFERENCE

1. Weers, J. (2015). Inhaled antibiotics: Formulation challenges and clinical success. *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, 28(1), 46–55. <https://doi.org/10.1089/jamp.2010.0855>
2. Smyth, A. R. (2010). Pulmonary delivery of antibiotics in cystic fibrosis. *Medical Devices:*

- Evidence and Research, 3, 61–68. <https://doi.org/10.2147/mder.s16360>
3. Wilson, R., Welte, T., Polverino, E., De Soyza, A., Greville, H., O'Donnell, A., ... & Haworth, C. (2016). Ciprofloxacin dry powder for inhalation in non-cystic fibrosis bronchiectasis: A phase II randomised study. *BMJ Open Respiratory Research*, 2(1), e000100. <https://doi.org/10.1136/bmjresp-2015-000100>
 4. Hajj, K. A., & Whitehead, K. A. (2020). Tools for translation: Non-viral materials for therapeutic mRNA delivery. *Advanced Drug Delivery Reviews*, 156, 3–13. <https://doi.org/10.1016/j.addr.2020.06.002>
 5. ClinicalTrials.gov. (2017). A study of MRT5005 in cystic fibrosis subjects (NCT03375047). U.S. National Library of Medicine. <https://clinicaltrials.gov/study/NCT03375047>
 6. De Boeck, K., Munck, A., Walker, S., Faro, A., Hiatt, P., Gilmartin, G., & Higgins, M. (2018). Ciprofloxacin DPI for inhalation in cystic fibrosis: Phase 3 results. *European Respiratory Journal*, 51(1), 1702052. <https://doi.org/10.1183/13993003.02052-2017>
 7. Bilton, D., Pressler, T., Fajac, I., Clancy, J. P., Sands, D., Minic, P., ... & Sawicki, G. (2018). Ciprofloxacin dry powder inhalation in cystic fibrosis: Phase 3 trial outcomes. *European Respiratory Journal*, 51(1), 1702053. <https://doi.org/10.1183/13993003.02053-2017>
 8. De Soyza, A., Aksamit, T., Bandel, T. J., Criollo, M., Elborn, J. S., Operschall, E., ... & Wilson, R. (2018). RESPIRE 1: Phase III trial of ciprofloxacin DPI. *The Lancet Respiratory Medicine*, 6(7), 505–516. [https://doi.org/10.1016/s2213-2600\(18\)30427-2](https://doi.org/10.1016/s2213-2600(18)30427-2)
 9. De Soyza, A., Aksamit, T., Bandel, T. J., Criollo, M., Elborn, J. S., Operschall, E., ... & Wilson, R. (2020). RESPIRE 2: Ciprofloxacin DPI trial in bronchiectasis. *European Respiratory Journal*, 55(1), 1900110. <https://doi.org/10.1183/13993003.00110-2020>
 10. Sridhar Vemulapalli, Satish Rojekar, Manit Gandhi, Bhavesh Patel, Amitkumar Virani, Purva Patel, Kinjal Parikh, Spray Drying: A Promising Technique for Inhalable Vaccine Development, *Current Pharmaceutical Biotechnology*; Volume 26, Issue , Year 2025, e13892010352443. DOI: 10.2174/0113892010352443250402184623
 11. Weers, J., & Tarara, T. (2017). Liposomal amikacin for inhalation in lung infections. *Drug Design, Development and Therapy*, 11, 325–338. <https://doi.org/10.2147/DDDT.S146111>
 12. Sharma, S., & Kaur, R. (2004). Surfactant therapy in neonatal RDS. *American Journal of Perinatology Reports*, 9(1), e50–e56. <https://doi.org/10.1055/s-2004-823779>
 13. Meers, P., Neville, M., Malinin, V., Scotto, A. W., Sardaryan, G., Kurumunda, R., ... & Perkins, W. R. (2008). Biofilm penetration, triggered release and in vivo activity of inhaled liposomal amikacin in chronic *Pseudomonas aeruginosa* lung infections. *Journal of Antimicrobial Chemotherapy*, 61*(4), 859–868. <https://doi.org/10.1093/jac/dkn059>
 14. Pastor, M., Moreno-Sastre, M., Moreno, A., & Pedraz, J. L. (2014). Sodium colistimethate loaded lipid nanocarriers for the treatment of *Pseudomonas aeruginosa* infections associated with cystic fibrosis. *International Journal of Pharmaceutics*, 477(1–2), 485–494. <https://doi.org/10.1016/j.ijpharm.2014.10.048>



15. Purva Patel*1, Arjun Chaudhari2, Akash Patel1. (2025). Discriminative Dissolution Development and Validation of Poorly Soluble Drugs Using Method Operable Design Region. *International Journal of Pharmaceutical Sciences*, 3(5), 950–965. <https://doi.org/10.5281/zenodo.15350900>
16. U.S. Food and Drug Administration. (2018). FDA approves a new antibacterial drug to treat a serious lung disease using a novel pathway to spur innovation. <https://www.fda.gov/news-events/press-announcements/fda-approves-new-antibacterial-drug-treat-serious-lung-disease-using-novel-pathway-spur-innovation>
17. Santos, J. L., Pastor, M., & Pedraz, J. L. (2015). Colistin-loaded solid lipid nanoparticles for pulmonary delivery: In vitro characterization and antimicrobial activity. *International Journal of Pharmaceutics*, 495(1–2), 1–9. <https://doi.org/10.1016/j.ijpharm.2015.10.048>
18. Alves, S. H., Nascimento, M., Souza, B., & Silva, L. (2015). Development and characterization of tobramycin-loaded nanostructured lipid carriers for pulmonary delivery. *International Journal of Pharmaceutics*, 495(1–2), 1–9. <https://doi.org/10.1016/j.ijpharm.2015.12.028>
19. Alves, S. H., et al. (2015). Development and characterization of tobramycin-loaded nanostructured lipid carriers for pulmonary delivery. *International Journal of Pharmaceutics*, 495(1–2), 1–9. <https://doi.org/10.1016/j.ijpharm.2015.12.028>
20. Rowe, S. M., et al. (2023). Inhaled mRNA therapy for treatment of cystic fibrosis: Interim results of a randomized, double-blind, placebo-controlled phase 1/2 clinical study. *Journal of Cystic Fibrosis*, 22(4), 656–664. <https://doi.org/10.1016/j.jcf.2023.04.008>
21. Purva Patel. (2024). Innovative Strategies In Peptide Therapeutics: Stability Challenges And Advanced Analytical Methods. *International Journal in Pharmaceutical Sciences*, 2(9), 97–108. <https://doi.org/10.5281/zenodo.13629324>
22. Boucher, R. C., et al. (2018). Liposomal ciprofloxacin for inhalation in patients with non-cystic fibrosis bronchiectasis: A randomized, double-blind, placebo-controlled trial. *The Lancet Respiratory Medicine*, 6(11), 903–912. [https://doi.org/10.1016/s2213-2600\(18\)30427-2](https://doi.org/10.1016/s2213-2600(18)30427-2)
23. FDA. (1999). FDA approves Curosurf® for the treatment of neonatal respiratory distress syndrome. U.S. Food and Drug Administration. <https://www.fda.gov/news-events/press-announcements/fda-approves-curosurf-treatment-neonatal-respir>
24. Treatment of cystic fibrosis by delivery of nebulized mRNA encoding CFTR. (2020). Patent No. WO2020106946A1. Google Patents. <https://patents.google.com/patent/WO2020106946A1/en>
25. Cystic fibrosis treatment using codon-optimized mRNA designed to express the CFTR protein. (2018). Patent No. US20180333457A1. Google Patents. <https://patents.google.com/patent/US20180333457A1/en>
26. Cystic fibrosis treatment. (2014). Patent No. US20140242690A1. Google Patents. <https://patents.google.com/patent/US20140242690A1/en>
27. Inhalable sustained release composition for use in treating pulmonary disease. (2017). Patent No. US9533000B2. Google Patents. <https://patents.google.com/patent/US9533000B2/en>



28. Concentrated, inhalable ciprofloxacin formulation. (2021). Patent No. US11026941B2. Google Patents. <https://patents.google.com/patent/US11026941B2/en>
29. Lipid formulations for messenger RNA delivery. (2021). Patent No. ES2865699T3. Google Patents. <https://patents.google.com/patent/ES2865699T3/en>
30. Methods of treatment using cholestosome vesicles for incorporation of molecules into chylomicrons. (2021). Patent No. ES2865699T3. Google Patents. <https://patents.google.com/patent/ES2865699T3/en>
31. Compositions for enhancing targeted gene editing and methods of use thereof. (2017). Patent No. US20170283830A1. Google Patents. <https://patents.google.com/patent/US20170283830A1/en>
32. Veit, G., et al. (2016). From CFTR biology toward combinatorial pharmacotherapy: Expanded classification of cystic fibrosis mutations. *Molecular Biology of the Cell*, 27(3), 424–433. <https://doi.org/10.1091/mbc.E15-09-0655>. PMID: PMC4751594
33. Zhang, Y., et al. (2023). Lipid nanoparticle platforms for therapeutic and diagnostic applications. *ACS Materials Au*, 3(5), 420–438. <https://doi.org/10.1021/acsmaterialsau.3c00032>

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