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REVIEW

Advances in Targeted Engineered Nanoparticle-Based Therapeutics for Respiratory Diseases: Current Insights and Future Perspectives

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Abstract: Treatments for respiratory diseases, including lung cancer, infectious pulmonary disease, acute respiratory distress syndrome (ARDS) and pulmonary fibrosis remain challenging. Conventional therapy such as inhaled corticosteroids and systemic antibiotics faces limitations of poor bioavailability, nonspecific biodistribution, and inadequate pulmonary barrier penetration, which often lead to suboptimal therapeutic outcomes. Engineered nanoparticles (ENPs) have recently gained significant attention as a potential solution to address these existing challenges. By encapsulating therapeutic agents within lipid-based, polymeric, or inorganic nanostructures, ENPs enable targeted delivery and controlled release, thereby minimizing systemic toxicity and increasing interactions with disease-specific cellular targets. Notably, inhalable ENPs targeting lung cancer cell receptors have demonstrated exceptional ability to penetrate lung barriers, evade clearance, and deliver drugs deep into lung tissue while significantly reducing systemic side effects. Recent advancements in nanotechnology have further broadened their applications in gene therapy, immune modulation and regenerative medicine, such as stem cell-derived extracellular vesicles (EVs) and hydrogel scaffolds for pulmonary tissue repair. This review elucidates therapeutic applications in respiratory diseases, summarizes current advances in formulation design, and discusses translational challenges including nanoparticle heterogeneity, inhalation barriers and gaps in clinical implementation such as reproducibility and scalability, and future directions for clinical translation including reproducibility.

Keywords: respiratory diseases, engineered nanoparticles, nanomedicine, drug delivery systems, targeted therapy, regenerative medicine, clinical translation

Introduction

The lungs, as one of the organs most frequently exposed to external environments, are susceptible to pathogens, environmental pollutants, tobacco exposure, genetic predisposition, and aging.[1,2] Acute respiratory distress syndrome (ARDS) is a severe and often fatal clinical syndrome resulting from various forms of pulmonary insult. It is typified by damage to the alveolar–capillary membrane, leading to widespread pulmonary edema and dysregulated inflammatory responses. Clinically, ARDS presents with persistent hypoxemia unresponsive to conventional oxygen therapy and progressive respiratory failure, with mortality rates surpassing 40%.[3] Pulmonary fibrosis, frequently arising as a sequela of prior acute pulmonary inflammation, is characterized by the gradual development of fibrotic remodeling within the lung parenchyma. This scarring is driven by abnormal fibroblast activation, epithelial–mesenchymal transition (EMT), and excessive deposition of fibrotic tissue. Dysregulated transforming growth factor β (TGF-β), Wnt/β-catenin, and hedgehog signaling pathways are widely recognized as central drivers of this process.[4] Pneumonia typically presents with alveolar inflammatory exudation, consolidation, and

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neutrophil infiltration. Lung cancer remains the foremost cause of cancer-related mortality globally and is predominantly classified into non-small cell lung cancer (NSCLC), accounting for approximately 85% of cases, and small-cell lung cancer. Long-term chemotherapeutics may result in neurotoxicity, hair loss, hepatotoxicity and nephrotoxicity. Although significant progress has been made in the development of targeted therapies and tyrosine kinase inhibitors (TKIs), disease progression continues due to the persistent issues of drug resistance and off-target effects.[5] Notable adverse effects of TKIs, especially cardiovascular events, are associated with imbalanced systemic and local drug biodistribution.[6] Agents such as pirfenidone and nintedanib, commonly prescribed for the management of pulmonary fibrosis, are known to induce side effects including gastrointestinal disturbances and pronounced diarrhea.[7] Thus, there is a pressing need for safe and efficient drug delivery systems as well as innovative therapeutic strategies with enhanced targeting capabilities to improve the management of respiratory diseases.

In recent decades, rapid advancements have been made in the field of nanotechnology, which offers innovative solutions to these existing challenges. Nanoparticles (NPs) are defined as solid supramolecular structures, typically sized between 10 nm and 500 nm. Including lipid-based, polymeric, inorganic, and bioderived formulations, NPs have demonstrated significant potential in treating tumors, infections, and ischemic diseases.[8–11] These nanoscale systems address critical limitations of conventional therapies by increasing drug solubility, prolonging blood circulation time, improving penetration across physiological barriers, and reducing systemic toxicity.[10,12] Furthermore, advanced engineering strategies have substantially optimized the therapeutic efficacy of NPs. For example, tissue- or cell-specific modifications enable localized drug accumulation at target sites to maximize therapeutic efficacy while minimizing dosage requirements.[13] Co-delivered or multidrug-loaded NPs exhibit superior pharmacokinetic profile characteristics, such as sustained release, and provide possibilities for multidimensional treatment strategies, including gene and chemotherapy, to cope with drug resistance.[14,15] Thus, NPs hold considerable promise in treating respiratory diseases. In this review, we summarize the therapeutic applications of NPs across major respiratory diseases, emphasizing their effects and mechanisms. In addition, we focus on feasible engineering strategies for enhancing the bioavailability and targeting potential of NPs.

Overview of Nanoparticle Formulations (NFs)

Nanotechnology was first elucidated by Richard Feynman in his lecture "There's plenty of room at the bottom". In 1976, Birrenbach and Speiser reported the preparation and in vitro characteristics of polymerized micelles containing drug molecules, bringing the concept of nanotechnology to reality.[16] The subsequent approval of the first liposomal doxorubicin (Doxil) by FDA in 1995 marked a pivotal transition toward clinical trials. This milestone further expands opportunities for nanomedicine in clinical research applications. One of the major applications is to utilize NPs for drug delivery and disease diagnosis.[17] Owing to their exceptionally small size, NFs possess numerous unprecedented advantages. They exhibit enhanced permeability across biological barriers in vivo, target specific cell types through the decoration of ligands, and improve drug uptake and release (Table 1 and Figure 1).[18] However, the potential toxicity of nanomaterials warrants serious consideration, particularly the oxidative stress resulting from elevated biological reactivity.[19]

Overall, natural nanoparticles hold significant promise in biomedicine, but their inherent properties often require engineering modification to improve their therapeutic performance. One of the key challenges is that natural

Table 1 Processing Methods and Characteristics of NFs from Different Sources

Product	Critical Material for Synthesis	Drug on Board	Nanomaterial Characteristic	Ref.
Patisiran	Dlin-MC3-DMA, DSPC, Cholesterol, PEG_{2000}-C-DMG	siRNA	Protect the siRNA from nuclease digestion; accumulate in the liver to regulate TTR protein production	Yuta Suzuki[20]
mRNA-1273	SM-102, DSPC, Cholesterol, PEG_{2000} -DMG	mRNA	High encapsulation efficiency; excellent biocompatibility; stability affected by pH, temperature	Rameswari Chilamakuri[21]

(*Continued*)

Table 1 (Continued).

Product	Critical Material for Synthesis	Drug on Board	Nanomaterial Characteristic	Ref.
CCM-CLN	Glycerol monostearate, Soybean phospholipid, CTAB, SDS	CCM	Target lung tissue cells; enhance vesicle stability and acquisition by tumor cells via surface-active ingredients	Songlin Li MD[22]
NanoTherm	Superparamagnetic iron oxide, amino silane	Fe_2O_3	Prolong blood circulation time; generate local hyperthermia to specifically kill cancer cells	Jan Grzegorzewski[23]
AuNR@mSiO_2-Dox NP	Au, Mesoporous silica	Dox	High two-photon absorption cross section; good biocompatibility; low toxicity; excellent cellular uptake performance	Jiangling He[24]
GC-PEI NP	GC, PEI, 5β-cholic acid, NHS, EDC, HSPyU	siRNA	Enhance stability with strongly positively charged surfaces; target tumors with higher efficiency	Myung Sook Huh[25]
PLGA-PEI NP	PLGA copolymer, PEI, polyvinyl alcohol, polyvinyl pyrrolidone	Paclitaxel, Stat3 siRNA	Sustained release effect; integrate anticancer drugs; reduce chemotherapy resistance	Wen-Pin Su[26]
PD-CSNP	Chitosan, TPP, Tween 80	PD	Nontoxic and biodegradable; increase the residence time in the absorption site; good sustained release performance	Adel Abdel-Moneim[27]

Abbreviations: DSPC, 1,2-Distearoyl-sn-glycero-3-phosphorylcholine; CTAB, cetyltrimethyl ammonium bromide; SDS, sodium dodecyl sulfate; CCM, curcumin; Dox, doxorubicin; GC, glycol chitosan; PEI, polyethylenimine; NHS, N-hydroxysuccinimide; EDC, 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride; HSPyU, dipyrrolidino(N-succinimidyloxy)carbenium hexafluorophosphate; PLGA, poly(lactic-co-glycolic acid); TPP, tripolyphosphate; PD, polydatin.

nanoparticles tend to have a broad size distribution, unstable surface charges, and limited solubility, all of which can restrict their bioavailability and targeting precision. For example, traditional herbal nanoparticles may have large sizes or lack functional surface groups, leading to inconsistent drug release profiles.[28] Additionally, cell membrane-derived nanoparticles have certain biocompatibility, but they may lack sufficient modification to achieve effective immune escape.[29] Therefore, surface engineering strategies including click chemistry, cross-coupling, and alkylation with silanes can greatly improve pharmacokinetics, targeting accuracy, and overall therapeutic effects.[30]

In the field of pulmonary disease treatment, inhalation administration is regarded as the preferred rapid and effective option, that was demonstrated during the COVID-19 pandemic.[31] However, the natural physical, chemical and immune barriers of the lungs clear traditional drugs to a certain extent in addition to their defensive functions (Figure 2). The pulmonary mucociliary apparatus captures and sweeps away the deposited drugs, while the macrophages and enzymatic barrier secreted by the pulmonary epithelial cells further degrade them.[32,33] Nanopreparations can diffuse within the mucus due to their small size, and through certain engineering strategies (such as glycoconjugation), they can modify their surface properties to overcome the barriers and show high absorbency.[34] Therefore, it is of great significance to shift the pulmonary nanomedicine delivery system from exploratory research to clinical application.

Liposome-Based Nanoparticles

As a pioneering nanomaterial, liposomes have been extensively applied in the encapsulation and delivery of various substances, especially oligonucleotides, DNA and mRNA antigens, and CRISPR components.[35] The conventional liposome is a bilayered spherical structure with a diameter ranging from 50 to 200 nanometers and is composed of phospholipids and cholesterol. It can be synthesized through multiple techniques, such as solvent dispersion with antisolvent addition, solvent evaporation, or detergent removal. The structural and size characteristics of the resulting liposomes are highly influenced by variations in temperature, duration, and the choice of solvents employed during fabrication.

Lipid nanoparticles (LNPs) are typically categorized based on their particle size and lamellarity. From largest to smallest, they include giant unilamellar vesicles (GUVs, >1000 nm), multivesicular liposomes (MVVs, >1000 nm), multilamellar vesicles (MLVs, >500 nm), oligolamellar vesicles (OLVs, 100–1000 nm), large unilamellar vesicles

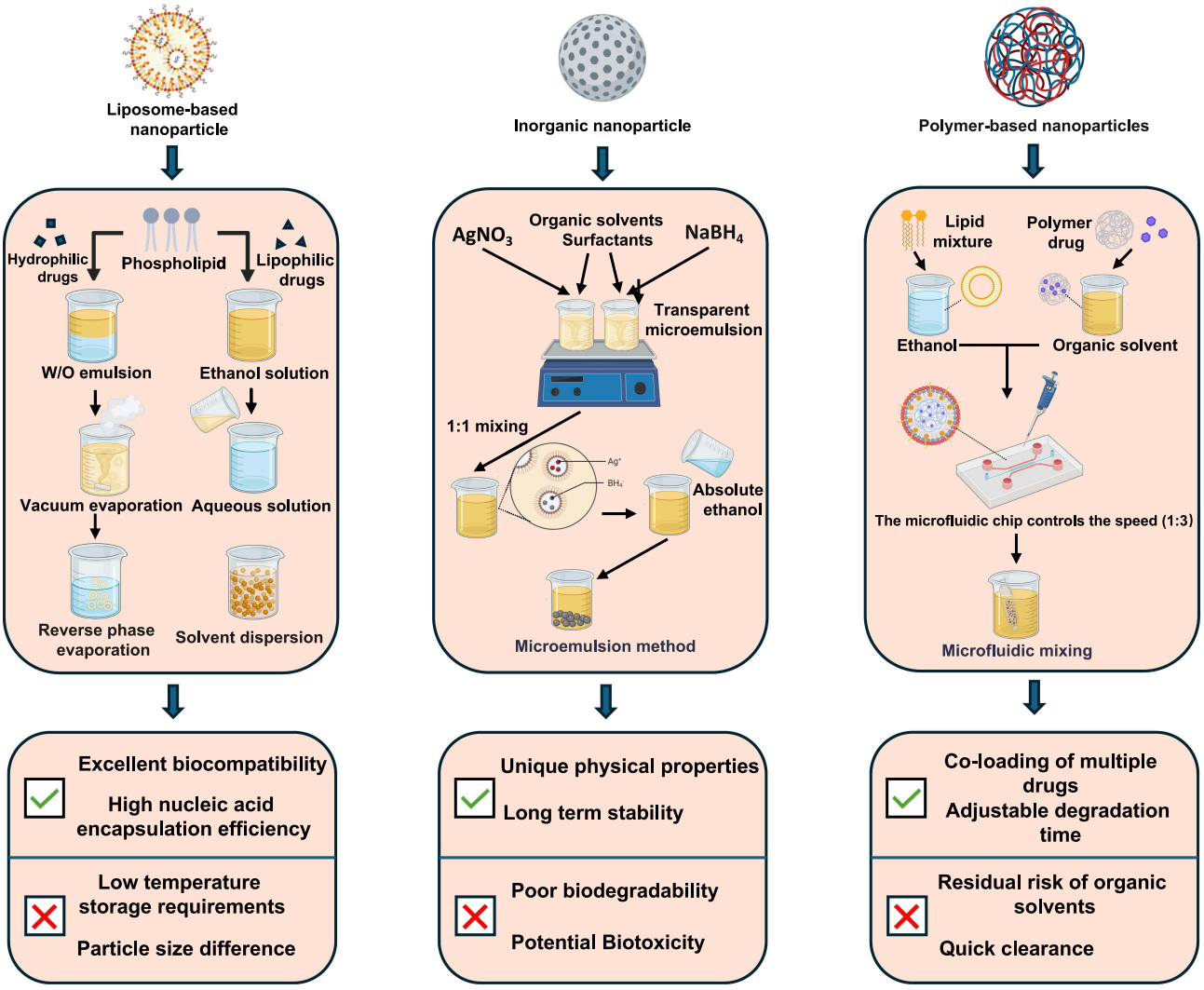

Figure 1 Acquisition approaches and biologic al properties of distinct nanoparticle types.

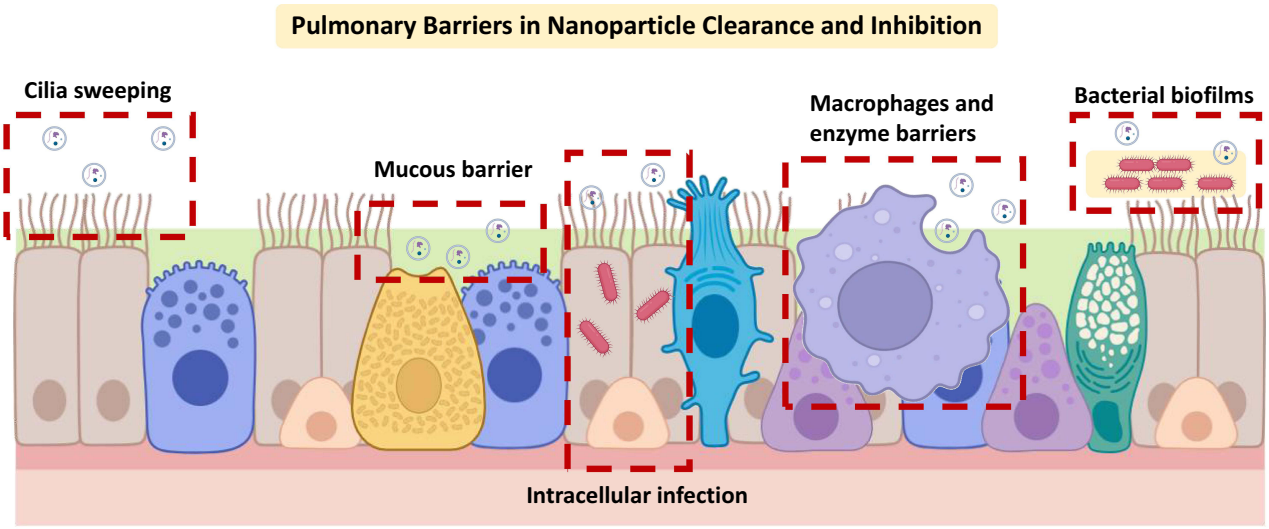

Figure 2 Primary mechanism of pulmonary barrier-mediated nanoparticle clearance and delivery inhibition.

(LUVs, >100 nm), and small unilamellar vesicles (SUVs, 20–100 nm).[36] The nanostructured lipid carriers (NLCs) and solid lipid nanoparticles (SLNs) produced by subsequent processes exhibit improved packaging and transportation efficiency under specific circumstances; for example, NLCs encapsulated with dexamethasone (Dex) can reach the distal alveoli and inhibit the NF-κB inflammatory pathway in ALI mice.[37]

Theoretically, the amphiphilic nature of phospholipids enables them to carry a wide range of drugs. However, the tendency of phospholipids toward mutual fusion or aggregation and their rapid clearance result in suboptimal performance.[38] Currently, surface modification represents the primary enhancement strategy. For example, the PEGylation of liposomes facilitates their evasion of immune phagocytosis, while targeted ligand modification enhances their specificity.[39] Although there may be a range of side effects, mainly allergic reactions, researchers have been looking for better alternatives similar to PEGylation.[40]

A common drawback of LNP-based systems is their preferential accumulation in the liver following systemic administration, largely due to the formation of a protein corona. To circumvent this limitation, Le et al designed a poly(β-amino ester) (PBAE)-lipid hybrid nanoparticle, which was able to preferentially transfect pulmonary endothelial cells. Mechanistic studies demonstrated that different protein coating layer compositions and favorable particle size/form helped achieve selective distribution in the lungs. Using these nanoparticles to deliver bevacizumab mRNA significantly enhanced local antibody production, inhibited VEGF-mediated angiogenesis, and suppressed tumor growth in an in situ non-small cell lung cancer model. This approach provides compelling evidence for the potential of the mRNA delivery system based on nanomaterials in targeted therapies for lung cancer.[41]

Inorganic Nanoparticles

Inorganic nanomaterials occupy an indispensable position in contemporary medical applications. On the one hand, the constituent particles exhibit a high degree of order and rigidity, which means that they demonstrate relatively weak spontaneous aggregation at the nanoscale compared with organic polymers. On the other hand, materials possess distinct optical, magnetic, and additional physical properties derived from their crystal structure and quantum confinement effect.[42] A typical example is the surface plasmon resonance effect of gold nanoparticles, which results in a characteristic absorption peak at approximately 520 nm, whereas superparamagnetic iron oxide nanoparticles can generate reversible magnetic moment alignment under an external magnetic field.[43,44] Currently, the synthesis of inorganic nanomaterials is accomplished primarily through the dissolution and precipitation of salts in various solvents. The hydrothermal synthesis method can produce homogeneous nanoparticles by controlling the crystal nucleation rate at high temperatures and pressures. The microemulsion method can be used to prepare quantum dot materials with excellent monodispersity by using a reactor formed by a surfactant.[45] These inorganics can be further precisely configured to obtain various sizes, structures, and geometries.

In the treatment of respiratory diseases, iron oxide nanoparticles have demonstrated a significant capacity to inhibit tumor growth in addition to serving as traditional contrast agents through polarizing macrophages to the M1 proinflammatory phenotype; peptide-coated hybrid gold nanoparticles (GNPs) have been demonstrated to inhibit the downstream TLR4 signaling pathway in phagocytes by preventing endosome acidification, thereby exhibiting anti-inflammatory effects; and mesoporous silica nanoparticles represent an optimal choice for drug delivery systems because of the possibility of decorating their external surface with molecules as gating mechanisms.[46–48] However, the intrinsic solubility and cytotoxicity challenges associated with inorganic nanoparticles significantly restrict their potential as conventional carriers. Studies have shown that metal nanoparticles activate the NLPR3 inflammasome through particle endocytosis, lysosomal damage and other pathways and mediate various inflammatory injuries.[49] Future research may focus on using surface modifications and engineered coatings to reduce direct contact between nanomaterials and living organisms, designing biodegradable biomaterials, and developing relevant theoretical models to simulate and predict toxicity.

Polymer-Based Nanoparticles

Polymer nanoparticles mainly take advantage of the amphiphilic properties of natural or synthetic polymers, such as the hydrophobic chain of poly (lactic-co-glycolic acid) (PLGA) and the hydrophilic end of polyethylene glycol (PEG), to construct nanostructures through precise and controlled physical and chemical methods. The mainstream synthesis

methods can be divided into solvent evaporation, emulsion diffusion, dialysis, and the utilization of supercritical fluids.[50] The products are mainly categorized as nanocapsules and nanospheres based on their specific structure. The former are designed with a "core–shell" structure to achieve high drug loading and prolonged release. Hydrophobic drugs can be efficiently contained in the oil core, and the outer polymer shell can achieve zero-order release kinetics through regulation of the degree of crosslinking. The latter are homogeneous matrix structures that protect degradable drugs such as mRNA through physical entanglement or chemical bonding of polymer chains.[51] For example, PEG-PLGA nanospheres protect siRNAs from nucleases and greatly improve the stability of their targeting.[52]

At present, the application of single polymeric nanomaterials in drug or gene delivery technologies has reached a relatively advanced stage of development. On this basis, improvement measures emphasize the hybridization of multiple nanomaterials.[53] Compared with their individual components, hybrid conjugates can synergistically integrate advantages while mitigating disadvantages. A prime example is lipid–polymer hybrid nanoparticles (LPHNPs), which exhibit superior biocompatibility and remarkable multidrug encapsulation capability. Therefore, LPHNPs can more effectively address the requirements of combination therapy in cancer treatment and antibiofilm strategies in antibacterial therapy, leading to their widespread application. For example, Pelinsu Korucu Aktas et al developed crizotinib-loaded PLGA-LPHNPs and PCL-LPHNPs, which achieve drug sustained release and targeting by controlling particle size. These formulations exert significant therapeutic effects on non-small cell lung cancer cells by activating caspase-3 to trigger cell apoptosis and blocking the tyrosine kinase activities associated with ALK and hepatocyte growth factor receptors. However, most of the current hybrid systems still face the challenge of large-scale production—the cost of equipment for preparing LPHNPs by microfluidic technology is tens of times greater than that of equipment for traditional emulsification methods.[54,55] This research field is still in its infancy, and several challenges need to be overcome to meet clinical expectations.

Therapeutic Potential of NFs and Engineering Strategies

Conventional therapeutic drugs have been complemented by the emergence of NPs as an effective therapeutic strategy for treating respiratory diseases. This is due to the ability of NPs to modulate substance metabolism, influence gene expression, and alter the cellular microenvironment.[56] However, naturally produced or synthesized NPs face limitations, including low bioavailability, poor targeting, high immunogenicity, high heterogeneity among batches, unstable effects, and numerous and unclear adverse effects. This has led to a growing interest in the engineering of modified NPs to increase their therapeutic potential.[57] Common engineering strategies include the use of artificially designed nanocomponent complexes, biofilm coatings, cargo encapsulation, and artificial scaffolds. The selection of a particular strategy is often informed by the therapeutic purpose, with surface modification aiming to enhance targeting and penetration, while cargo encapsulation improves the stability and bioavailability of drugs in vivo (Figure 3).[58] The employment of a range of engineering methodologies for ENPs has been demonstrated to increase their therapeutic efficacy while concomitantly providing novel approaches to address respiratory diseases for which conventional therapeutic modalities have proven ineffective.[59]

Pneumonia and Infection

Infectious diseases of the lungs, typified by community-acquired pneumonia (CAP), may result in sepsis and acute respiratory distress syndrome. The most prevalent pathogens identified include *Klebsiella pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae*, human rhinovirus, influenza A virus, *Streptococcus pneumoniae, Staphylococcus aureus*, adenovirus, respiratory syncytial viruses, and *Legionella pneumophila*.[60] Previous treatment protocols have indicated that hospitalized patients with suspected bacterial CAP, who do not present risk factors for resistant pathogens, may be appropriately treated with a combination of β-lactam and macrolide antibiotics, such as ceftriaxone and azithromycin, for at least three days.[61] Furthermore, corticosteroids have been demonstrated to promote patient survival and enhance clinical outcomes.[62] Conventional antibiotic-focused treatment regimens, while effective at suppressing pathogenic bacteria, still do not adequately inhibit the inflammatory response or mitigate tissue damage. The issue of antibiotic resistance is another problem that traditional therapies must address. Bacteria have been observed to develop increasingly strong resistance, and even multidrug resistance, by modifying or degrading antibiotics to inactivate them, modifying or altering drug binding sites within bacteria, strengthening efflux mechanisms to expel drugs from bacteria,

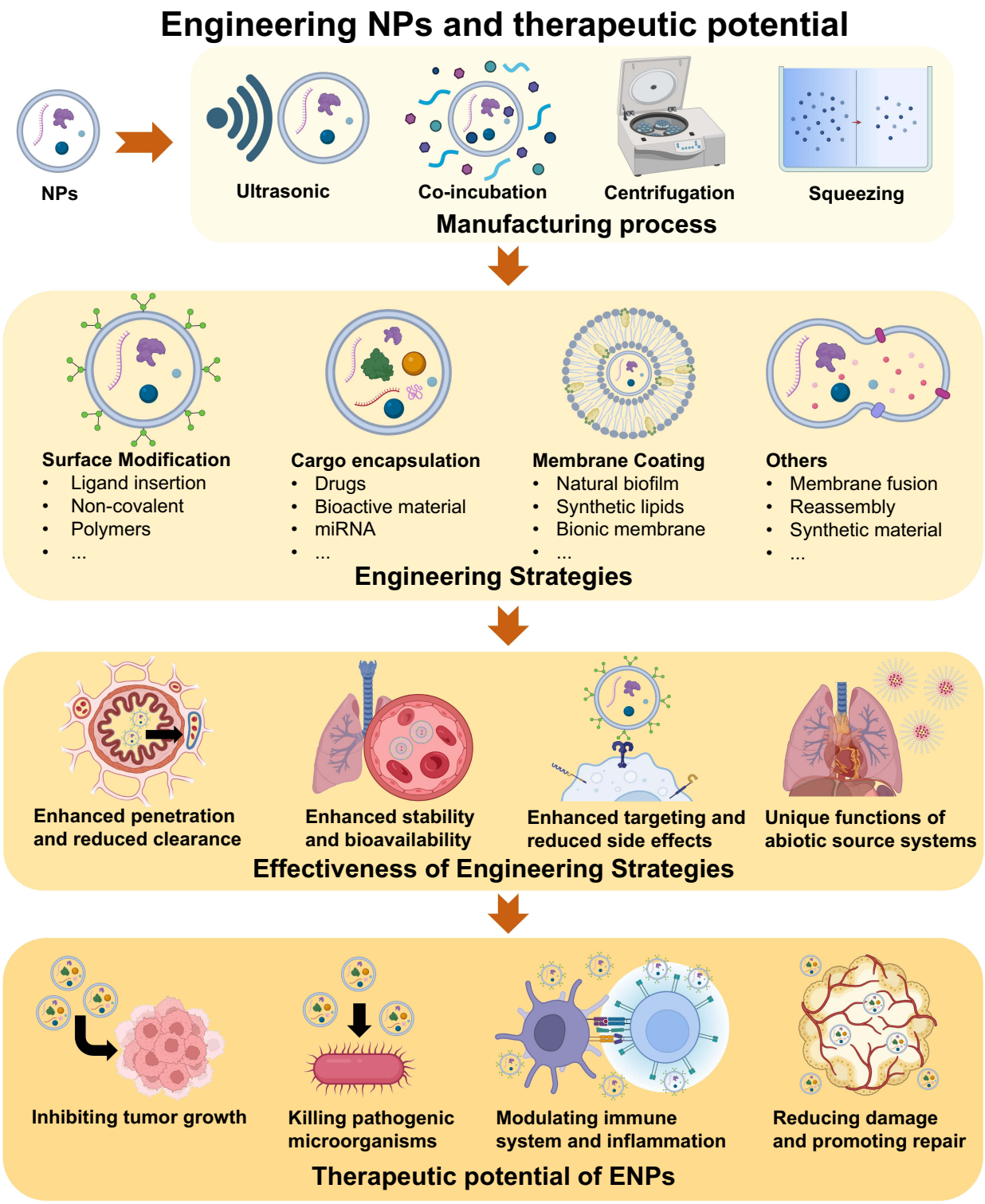

Figure 3 Strategies for ENPs engineering and therapeutic potential.

and reducing the ability of antibiotics to penetrate microbial cells.[63] It is evident that NPs represent the most efficacious method for the elimination of multidrug-resistant bacteria. This is due to the fact that they function as carriers for natural antibiotics and antimicrobial agents, as well as active agents against bacteria. Furthermore, the surface engineering of nanocarriers offers significant advantages for targeting and altering various drug resistance mechanisms.[64] Concerns

regarding ototoxicity and nephrotoxicity have been raised with regard to the administration of such regimens.[65,66] Peter S Steyger hypothesizes that this phenomenon is associated with the non-specific transport of drugs to the inner ear, and that aminoglycoside permeable channels and non-receptor-mediated endocytosis of hair cell apical and synaptic membranes may play a significant role in this process.[67] The enhancement of treatment programs through the utilization of ENPs has the potential to yield favorable outcomes for CAP (Table 2).

Focusing on the direct therapeutic or drug delivery effects of NPs, numerous studies have employed the principles of immune microenvironment modulation, direct inhibition or killing of pathogens, and induction of artificial active immunity. Zhu et al proposed a clinical approach for managing severe acute respiratory syndrome associated with SARS-CoV-2 infection, centered on the use of nebulized exosomes derived from umbilical cord mesenchymal stem cells (MSCs). Exosomes isolated and purified via ultrafiltration demonstrated therapeutic efficacy, contributing to the resolution of pulmonary lesions and a shortened duration of hospitalization in patients with mild COVID-19 pneumonia. These beneficial

Table 2 Engineering Strategies and Enhanced Therapeutic Effects of ENPs in Pneumonia and Infection

Origin	Engineered Manufacturing Method	Disease Model	Modification Effect	Therapeutic Effect or Function	Ref.
PACE	Adding end groups for modification and encapsulation of mRNAs	SARS-CoV-2	Enhancing transfection efficiency by promoting the release of mRNA from endocytosed nanoparticles into the cytoplasm through improved endosomal escape mechanisms	Stimulating the activation of circulating antigen-specific $CD8^+$ T cells and the generation of lung-resident spike protein-specific tissue memory $CD8^+$ T cells	Alexandra Suberi[68]
PLGA	Coating neutrophil membranes, loading antibiotics and attaching microalgae	VAP	Reducing immune clearance of drugs and increasing active, targeted drug delivery	Effective in reducing *Pseudomonas aeruginosa* loads and significantly reducing animal mortality	Fangyu Zhang[69]
LNPs	Conjugating F4/80 antibody to LNPs loaded with siRNA	Respiratory viral infections	Improving the efficiency of siRNA delivery against macrophages	Attenuating local lung inflammation and promoting lung regeneration and repair	Gan Zhao[70]
SF-SANPs	Encapsulating rOmpA	*K. pneumonia* lung infection	Improving the optimization of protein encapsulation efficiency, improving mucosal adhesion properties, and increasing stability in biological fluids	Use as a promising vaccine against *Klebsiella pneumoniae*	Shahla Shahbazi[71]
JNPs	Carrying anti-inflammatory drugs or antibiotics at different structural thresholds	*P. aeruginosa* pneumonia	Reducing drug interactions and improving treatment efficiency	Reducing inflammation and inhibiting bacterial growth	Xiangjun Chen[72]
Cs-cas	Piggybacking naringenin through self-assembly method	*P. aeruginosa* pneumonia	Improving water solubility and bioavailability of naringenin	Reducing bacterial load in the lungs and decreasing the release of proinflammatory factors	Changquan Chen[73]
NK cell membrane-derived NPs	Encapsulating ITIC and cefoperazone	*K. pneumonia* lung infection	Evading macrophage capture, effectively navigating through mucus layers, and targeting the infection site	Enhancing the effectiveness of antibiotic therapy	Yue Wang[74]

Abbreviations: PACE, poly(amine-*co*-ester); PLGA, poly (lactic-*co*-glycolic acid); VAP, ventilator-associated pneumonia; LNP, lipid nanoparticle; K. pneumonia, *Klebsiella pneumoniae*; SF-SANPs, silk fibroin-sodium alginate nanoparticles; rOmpA, outer membrane protein A; JNPs, Janus nanoparticles; Cs-cas, chitosan-casein nanoparticles; ITIC, indacenodithi-eno[3,2-*b*] thiophene.

effects are presumed to be mediated by the delivery of bioactive molecules—such as mRNAs, miRNAs, and proteins—and through mechanisms involving anti-inflammatory activity and modulation of airway remodeling. This study offers a foundational framework and empirical support for the potential of nanoparticle engineering in therapeutic applications.[75–78]

Artificially synthesized and modified ENPs have significant advantages over their original nanomaterial counterparts in terms of targeted drug delivery, removal of virulence factors, inhibition of pathogen growth, and synergistic effects with other drugs.[79,80] The field of research focused on the development of precision inhalation delivery systems for antibiotics to treat pulmonary infections has attracted significant scientific interest. Alison Tatiana Madrid Sani et al developed a dry powder formulation for pulmonary delivery of azithromycin-loaded nanoparticles. The azithromycin was encapsulated within polycaprolactone nanoparticles, which had been functionalized with phospholipids that were rich in dipalmitoylphosphatidylcholine. The formulation was then produced as a fine powder by means of spray drying with monohydrated lactose. The mean hydrodynamic diameter of the nanoparticles obtained by the emulsion/solvent diffusion-evaporation technique was found to be in the range of 195–228 nm, exhibiting a narrow monomodal size distribution with a polydispersity index (PdI) of less than 0.2. The characterization of this ENP in terms of chemical structure, thermal analysis, and particle size has revealed that its aerosol properties demonstrate excellent aerodynamic performance, thus rendering it suitable for pulmonary inhalation drug delivery. Furthermore, microbiological assays demonstrated that the formulation retained the antimicrobial activity of azithromycin against Staphylococcus aureus and Streptococcus pneumoniae strains. In comparison with both oral and parenteral routes, the inhalation route offers a number of advantages, including the avoidance of first-pass hepatic metabolism, rapid diffusion in the lower respiratory tract, faster local therapeutic effects, higher efficacy, and lower doses. This, in turn, results in a reduction in direct drug exposure to other organs and a minimization of side effects. It is evident that dry powder formulations with stable encapsulation effects and particle size and structure matched to aerodynamic effects can serve as a new platform for antibiotic delivery in pulmonary infections. This offers a potential alternative treatment for respiratory infections via inhalation therapy.[81]

Membrane encapsulation is also considered a viable strategy for engineering modified NPs. This approach is usually based on biofilms with good biocompatibility and biosafety. Jin et al developed tea polyphenol-loaded nanoparticles (TP-NPs) utilizing an emulsification–evaporation technique. Following nanoparticle fabrication, platelet membranes (PM) were isolated and subsequently coated onto the surface of the TP-NPs, resulting in the formation of biomimetic nanoparticles denoted as PM \@TP-NPs. In this study, platelet membrane-derived vesicles were utilized to mask TP-loaded NPs, thereby exemplifying cell membrane stealth, an emerging biomimetic nanotechnology. Notably, compared with traditional drug delivery systems, platelet cell membranes are capable of replicating the complex physicochemical properties and bionic functions of the parent cell source, thus circumventing immune rejection. Furthermore, these membranes possess a natural ability to target inflammation. This delivery system has been demonstrated to deliver tea polyphenols with high precision, thereby suppressing lung inflammation, as evidenced by decreased lung vascular permeability, inhibition of NLRP3 activation, decreased IL-1β production, and reduced infiltration of airway and lung tissues, among others, compared with TPs or unmodified TP-NPs.[82] In addition to cell membranes with good biocompatibility, bacterial membranes that retain antigenic properties are also emerging as a new specific immune induction strategy. Mina Mehanny proposed a spray-drying vaccine production process for the prevention and control of pneumococcal disease. This process allows for the storage and transportation of biological products without the need for strict cold chain conditions, thereby extending their shelf life. The formulation of spray-dried gram-positive pneumococcal MVs-loaded vaccine microparticles involves the use of lactose and leucine as inert carriers. This approach is intended to enhance the stability and delivery of the vaccine for the purpose of pulmonary immunization. Confocal microscopy analysis verified the effective incorporation of the Streptococcus pneumoniae bacterial membrane into the fabricated particles, which were characterized by nanocrystalline structural features. This non-conventional immunization strategy has been shown to elicit potent pulmonary mucosal immune responses. Pulmonary mucosal vaccination is associated with multiple advantages, including an extensive epithelial surface area, a high density of antigen-presenting cells, and the abundant presence of secretory immunoglobulins. However, the pulmonary administration route still faces the problem of high pulmonary mucus and ciliary clearance rates. The development of aerodynamic designs and other biological strategies to enhance the deposition rate of ENPs in the lungs remains a research priority.[83]

It is widely acknowledged that mRNA vaccines represent a significant advance in the field of infectious disease prevention, owing to the expeditious development and enhanced safety they offer in comparison to conventional vaccine

methodologies, such as attenuated viruses. The most recent advancement in the domain of mRNA vaccine administration involves the utilization of lipid nanoparticle (LNP) formulations, which represent an engineered strategy that targets LNPs. These formulations serve to provide protection and enhance the delivery of mRNA vaccines within the body, with the objective of achieving favorable clinical outcomes.[84,85] BNT162b2 constitutes a lipid nanoparticle formulation of nucleoside-modified RNA (modRNA) encoding the full-length severe acute respiratory syndrome-CoV-2 spike protein. Fernando P. Polack et al confirmed the safety and efficacy of the two-dose regimen of BNT162b2 (30 μg per dose, administered 21 days apart) through global Phase 1/2/3 clinical trials. The findings indicated that the two-dose regimen is 95% effective against the novel coronavirus, SARS-CoV-2, which causes the disease known as "Covid-19". The administration of two 30-microgram doses of BNT162b2 has been demonstrated to elicit elevated levels of SARS-CoV-2 neutralizing antibody titers, in conjunction with substantial antigen-specific CD8+ and Th1-type CD4+ T cell responses. It is noteworthy that the occurrence of safety-related adverse events is transient, with a resolution occurring within days of their initial onset.[86]

Ionizable lipids are considered to be the most significant component of mRNA vaccine carriers and one of the future directions for engineering strategies. Present study aims to identify the optimal lipids that can enhance expression and provide a better immune response in mRNA-LNP vaccines, while maintaining low toxicity characteristics.[87] Wen Jie Melvin Liew developed a novel nanoparticle system using a combination of two key elements: firstly, a nanoparticle system based on a novel method of ionic gelation using a combination of a synthetic polymer (namely, methacrylate-modified chitosan (CMA)) and sodium tripolyphosphate (TPP), and secondly, a method of coating mRNA with synthetic lipids and cell membranes. These newly developed ionizable lipids enhance control over the release curve of encapsulated biomolecules, thus overcoming the burst release issues commonly found in traditional delivery systems. Furthermore, they allow for the coating of these soft nanoparticles with cell membranes or extracellular vesicles, thus expanding their potential applications in targeted and sustained biomolecular delivery.[88]

Cancer

Lung cancer is a prevalent malignancy that results in significant morbidity and mortality rates on a global scale. Conventional anticancer therapies, such as chemotherapeutic agents, photosensitizers, and immunomodulatory compounds, encounter substantial obstacles related to both therapeutic efficacy and safety. These issues encompass rapid systemic elimination, limited therapeutic windows, suboptimal tumor targeting, and significant off-target toxicity.[89]

The conventional chemotherapeutic agents employed in the treatment of cancer are characterized by their ability to target rapidly proliferating cancerous cells. However, these agents also exert an impact on normal cells that exhibit high levels of proliferation, a phenomenon that frequently gives rise to deleterious side effects. These adverse reactions may necessitate a reduction in the administered dosage or, in extreme cases, the complete cessation of treatment. This unfavorable outcome is primarily attributable to the substandard delivery precision of these pharmaceuticals.[90] Drug resistance is defined as the ability of tumor cells to develop mechanisms to overcome and resist the cytotoxic or inhibitory effects of chemotherapy drugs, thereby reducing the effectiveness of chemotherapy.[91] The utilization of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (EGFR-TKIs) serves as a pertinent exemplification. It has been demonstrated that exposure to epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) exerts pressure on tumors, thereby prompting them to evade cell death and develop resistance to treatment. The phenomenon of escape mechanisms manifests through the occurrence of gene mutations and amplifications, which are either selected or acquired.[92] Higher doses and more frequent administration have been shown to mitigate the adverse consequences of gradually developing cancer resistance. However, this may lead to increased toxicity and reduced patient survival rates. The combination of two or more chemotherapy drugs has been shown to enhance the efficacy of traditional chemotherapy by reducing the incidence of resistance.[93] However, this approach has not yet eliminated the side effects associated with non-specific uptake by normal cells. Consequently, the development of low-dose, high-efficiency, and precise drugs and drug delivery systems that reduce adverse reactions and resistance while enhancing treatment efficacy is of particular importance in the chemotherapy of lung cancer.[94]

To overcome these challenges, the development of innovative therapeutic and delivery systems capable of improving both efficacy and safety is imperative (Table 3). In particular, drug molecules, in their unmodified chemical form, have

Table 3 Engineering Strategies and Enhanced Therapeutic Effects of ENPs Applied in Lung Cancer Treatment

Origin	Engineered Manufacturing Method	Disease Model	Modification Effect	Therapeutic Effect or Function	Ref.
Fe_3O_4	Multilayered coating with tetraethyl orthosilicate, etc.	Lung metastatic breast cancer	Targeted delivery of Dox to tumors via magnetic field-guided mechanisms and size-driven, electrical interaction	Strong anti-tumor activity against 4T1 and A549 cells	Shan Shi[101]
Fe_3O_4	Surface modification with Tf	Adenocarcinoma of the lungs	Enhancing specific binding and targeted delivery	Combining photothermal therapy and delivery of miR-15a-5p for the treatment of lung cancer	Xiaoxu Lan[102]
Iron Oxide	Rational fabrication of superparamagnetic iron oxide nanoparticles encapsulated within core-cross-linked polymeric micelles through the application of ultrasound and chemical cross-linking agents	NSCLC	Remodeling of the lung TME, recruitment of CD8-T cells, and stimulation of TAM to secrete reactive nitrogen and cytokines with tumor-killing activity	Slowing tumor growth and delaying development of drug-resistant tumors	Natalie K Horvat[103]
AuNPs	Loading siRNA modified with sulfhydryl groups	Glucose starvation therapy in lung cancer	Delivering siRNA against Glut1 using miR-21 to trigger a targeted strand displacement reaction	Suppressing cancer cell proliferation and xenograft tumor development while inducing apoptosis by triggering glucose deprivation and reactive oxygen species (ROS)-mediated cascade signaling pathways	Jiaqi Li[104]
MPDA	Loading PE by electrostatic attraction and encapsulation with PVP	NSCLC	Accelerating PE release due to superior heat and light conversion properties	Increasing intracellular ROS levels in NSCLC cells	Jian Xu[105]
BP	Binding of Cy5 biotin-labeled BP to cancer cell membranes	NSCLC	Enhancing the targeted delivery of gefitinib to tumor sites and extending its intratumoral retention duration	Suppressing NSCLC cells and xenograft tumors	Zhongxiao Lin[106]
Albumin protein	Dox-loaded bovine serum albumin nanoparticles synthesized using desolvation methods	Lung cancer	Targeting drug release using changes in pH of the tumor microenvironment	Effective killing of lung cancer cells	Ahmed Aziz[107]
LNP	Incorporating a finely tuned proportion of negatively charged peptide–lipid conjugates into the conventional four-component lipid nanoparticle (LNP) formulation	Metastatic lung cancer	Assisting in charge stabilization and improving mRNA delivery efficiency after inhalation	Immunotherapeutic vaccines aimed at the prevention and treatment of cancer	Shuai Liu[108]
LCNs composed of MO	Ultrasonic processing to load berberine	Human lung epithelial carcinoma	Improving berberine bioavailability and enhancing drug stability and slow drug release	Involving the EMT pathway to inhibit tumor proliferation and migration	Keshav R Paudel[109]

(*Continued*)

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Table 3 (Continued).

Origin	Engineered Manufacturing Method	Disease Model	Modification Effect	Therapeutic Effect or Function	Ref.
Tetrandrine-loaded PTeNPs	Encapsulation using bionic platelet membranes	NSCLC	Reducing the extent of phagocytic clearance of drug active ingredients by macrophages, improving drug biocompatibility and active targeting ability	Inhibiting tumor cell growth	Hui Jiang[110]
CAR-T-cell-derived exosome-like nanovesicles	PTX loading using electroporation	NSCLC	Enhancing targeted drug delivery through active recognition and passive movement	Inhibiting tumor growth and reducing adverse effects	Wei Zheng[111]

Abbreviations: Dox, doxorubicin; Tf, transferrin; NSCLC, non-small cell lung cancer; TME, tumor microenvironment; TAM, tumor-associated macrophage; AuNPs, gold nanoparticles; Glut1, glucose transporter protein-1; ROS, reactive oxygen species; MPDA, mesoporous polydopamine; PE, pemetrexed; PVP, polyvinyl pyrrolidone; BP, black phosphorus; Cy5, cyanine 5; LNPs, lipid nanoparticles; LCNs, liquid crystal nanoparticles; MO, monoolein; EMT, epithelial–mesenchymal transition; PTeNPs, polycaprolactone-*b*-poly(ethylene glycol)-*b*-polycaprolactone nanoparticles; PTX, paclitaxel.

the potential to spontaneously assemble into homogeneous nanoparticles. These self-assembled or coassembled nanoplatforms have the dual functionality of acting as both carriers and drugs, which could help solve problems related to tumor metastasis and drug resistance.[95] Bi et al developed a prodrug known as fluplatin, which consists of cisplatin and fluvastatin. Subsequently, Fluplatin@PEG-PE NPs can be constructed by the self-assembly and poly(ethylene glycol)-phosphoethanolamine (PEG-PE) encapsulation of fluplatin. This engineering technique for the self-assembly of pure drug molecules is distinct from that of conventional nanovesicles in that its simple and reproducible production process assists in the elimination of bottlenecks from nanomedicine development, including quality control, scaled production, and clinical translation, while requiring no or only a small amount of surfactant to enhance the colloidal stability of PDNA.[96] This study demonstrates that fluvastatin mitigates cisplatin resistance induced by cisplatin-induced p53 mutations by downregulating the expression of oncogenes within the p53 downstream signaling pathway. This suggests that the synergistic effects of PDNA are significant.[97] The prospect of dual-pure drug nanoassemblies (DPDNAs) is not limited to the simultaneous modulation of multiple sites for therapeutic purposes but also extends to the integration of multiple therapies, such as the combination of chemotherapy and immunotherapy.[95] For example, the therapeutic efficacy of immune checkpoint blockade (ICB) immunotherapy may be constrained by the immunosuppressive tumor microenvironment (ITM).[98] Conversely, low-dose paclitaxel (PTX) has been shown to reduce the number of intratumoural infiltrating regulatory T cells (Tregs) and to suppress Treg-associated immunosuppression.[99] In this context, PTX-ICG nanoassemblies combining PTX with indocyanine green (ICG) have been designed for triple therapy with immunotherapy, light and chemotherapy. PTX-ICG ENPs exhibit excellent colloidal stability and are amenable to lyophilization for extended storage. When combined with α-PD-L1 therapy, PTX-ICG NPs effectively prevent tumor recurrence by enhancing cytotoxic T lymphocyte (CTL) infiltration into the tumor microenvironment via photodynamic therapy (PDT)-induced immunogenic cell death (ICD), while concurrently suppressing regulatory T cell (Treg) recruitment to mitigate immunosuppressive tumor microenvironments (ITMs).[100]

Within the domain of targeted drug delivery, ENPs are frequently utilized in conjunction with approaches such as receptor-mediated targeting, passive accumulation in pathological tissues, and activation through stimuli-responsive systems to enhance delivery precision.[112,113] Receptor-based targeting, a prevalent modification strategy, centers on the surface structure of modified nanocarriers and receptor-mediated endocytosis to achieve the selective elimination of tumor cells.[114] Matte Kasi Viswanadh was responsible for the design of a class of chitosan nanoparticles which were loaded with docetaxel (DTX) and modified with cetuximab (CTX). It has been demonstrated that, owing to its cationic nature, the final nanoparticle formulation exhibits a strong positive zeta potential. This property serves to enhance the uptake of negatively charged cancer cells by the nanoparticles. CTX is a monoclonal antibody of the latest generation that targets the epidermal growth factor receptor (EGFR). It binds to the extracellular domain of the receptor, resulting in the downregulation of both antibody-dependent and cell-mediated receptors. In addition, it induces cell death associated with receptor functional inhibition. DTX has been demonstrated to exhibit broad-spectrum antitumor activity. In the context of ENPs, the utilization of vitamin E PEG succinate (TPGS) as an emulsifier is a salient strategy that facilitates the attainment of optimal particle size and solubility for the nanodrug, thereby ensuring enhanced stability. In vitro investigations on A549 cells have indicated that the significant enhancement in NP-targeted toxicity may be ascribed to the elevated particle uptake via augmented sustained release of DTX through bioadhesion and EGFR-mediated endocytosis. The electrical properties and antibody specificity of these ENPs ensure excellent biological performance, with dual targeting capabilities. The loading of other chemotherapeutic drugs has been demonstrated to enhance the therapeutic effects of the ENPs themselves. Furthermore, the stable cross-linking and formulation of the ENPs opens new prospects for their clinical application.[115]

Passive targeting is predicated on the enhancement of penetration and retention (EPR) effect. This may facilitate the penetration of ENPs into the tumor stroma, and in addition, this enhanced penetration in newly generated blood vessels improves retention time. Physicochemical modifications, including charge, particle size, and surface-associated chemistry, have the capacity to enhance passive tumor targeting based on the EPR effect.[116] Notably, the use of natural cell membrane-encapsulated biomimetic nanoformulations can also be considered an emerging engineering strategy for passive targeting.[117–119] Poly(lactic-co-glycolic acid) (PLGA) nanoparticles loaded with paclitaxel (PTX) and camouflaged with A549 lung cancer cell membranes (AM\@PTX-NPs) exhibited progressive accumulation at the tumor site

over time, likely owing to the EPR effect associated with their nanoscale dimensions. Additionally, the E-calmodulin on the nanoparticle surface, inherited from the A549 membrane coating, further promoted cellular internalization following targeted delivery.[120]

The distinct intracellular composition of tumor cells, along with specific characteristics of the tumor microenvironment—including hypoxia, elevated temperature, acidic pH, and high glutathione concentrations—serve as key triggers for the design of stimuli-responsive targeting systems. The utility of such engineered approaches is predicated on the design of ENPs whose release rate is modulated by exposure to specific stimuli or that tend to respond to particular stimuli.[112] The application of artificially induced stimulus conditions has been demonstrated to elicit a comparable response, thereby broadening the scope for the engineering of this scheme. Enzyme-responsive systems can be regarded as a particular illustration of this notion. The occurrence of certain enzymes within the tumor microenvironment has been well documented, and these biomolecules have been exploited as triggers for the site-specific liberation of therapeutics from enzyme-mediated delivery systems. In this context, Tagami described the design of hybrid liposomal ENPs formulated from phospholipids in conjunction with poloxamer 188, tailored to respond to phospholipase A_2 (PLA_2), an enzyme aberrantly upregulated in malignant tissues. Exposure to PLA_2 catalyzed a marked acceleration in payload release, yielding an approximately eightfold increase compared with baseline conditions. Such enzyme-responsive ENPs present a promising platform for the encapsulation of therapeutic nanocrystals and their targeted deployment via pulmonary administration, thereby facilitating localized chemotherapeutic delivery within cancerous lesions.[121] Additional evidence indicates that various physical stimuli can serve as modulators of site-specific drug delivery. Among these, magnetic fields, when applied as external stimuli, have been shown to facilitate targeted transport processes. In a representative example, Park engineered magnetite nanocrystal clusters by integrating PEG–polyethylenimine–DOPA (dopamine) with magnetic ENPs. These clusters enabled magnetically driven intracellular translocation of encapsulated small interfering RNA (siRNA) into malignant cells.[122]

Nanocarrier-mediated drug delivery strategies involving the loading of other applicable therapeutic drugs using liposomes, polymer nanoparticles, dendrimers, nanoemulsions, micelles, carbon nanotubes, and gold nanoparticles as carriers have become among the most direct and effective strategies for developing ENPs.[112] The efficacy of ENPs as carriers is determined by the types of drugs delivered. Le et al developed a pGPU6/GFP/Neo STAT3-shRNA (pDNA) recombinant plasmid, which was constructed with STAT3 as a precise target. They subsequently synthesized multifunctional vitamin E succinate-chitosan-polyethylene glycol monomethyl ether histidine (VES-CTS-mPEG-His, VCPH) micelles encapsulating adriamycin (Dox). The dual-loaded nanoparticles (Dox/VCPH/pDNA) not only functioned as gene carriers but also mediated the transfection of the recombinant plasmid pDNA containing STAT3-shRNA into nude mice. This resulted in successful delivery of the recombinant plasmid to inhibit the transcription of STAT3 and achieve gene silencing. Furthermore, the nanoparticles exhibited the antitumor activity of adriamycin, thereby allowing the two drugs to synergistically inhibit the growth of tumors. The combination of these two drugs has been shown to enhance the inhibitory effect on tumor growth and tumor cell proliferation.[123] In the context of delivering biologically active substances such as DNA, siRNA or mRNA, the primary objective of engineering is to ensure stability and functionality to elicit their intrinsic effects.[124] Xu et al utilized a high-throughput combinatorial strategy to construct and evaluate engineered nanoparticles (ENPs) with the capacity for efficient cyclic RNA (circRNA) delivery to pulmonary tumor sites. CircRNAs encoding interleukin 12 (IL-12) elicited potent immune activation and substantial tumor regression in a Lewis lung cancer model. These findings suggest that H1L1A1B31 is a bifunctional lipid that promotes the efficient delivery of circRNAs and actively stimulates innate immune activation upon injection. It exhibits a transfection efficacy that is superior to that of the industry benchmark ALC-0315 LNP. Furthermore, compared with mRNA, the IL-12 circRNA LNPs demonstrate enhanced stability and sustained IL-12 expression. This renders them optimally suited to improve the TME through continuous IL-12 expression.[125] In addressing the challenge of selective organ targeting, Sean A. Dilliard postulated that the deliberate incorporation of a quaternary ammonium lipid into a lipid nanoparticle (LNP) formulation, at an optimized proportion, could enable endogenous mRNA delivery to pulmonary tissue. Empirical studies have demonstrated that introducing a quaternary ammonium lipid with a permanent cationic charge—constituting 50% of the total lipid composition and functioning as a selective organ targeting (SORT) moiety—effectively reprograms the biodistribution of mRNA from hepatic accumulation to preferential localization in the lungs. This redirection is attributed

to the formation of a protein corona exhibiting a distinctive enrichment pattern of plasma proteins, which are not implicated in liver-targeted delivery. This will provide a solid foundation for the rational design and optimization of formulation components, ensuring minimal delivery to off-target tissues. Furthermore, it will elucidate the use of endogenous proteins for organ-targeted nanoparticle drug delivery.[126]

Regenerative Potential

Acute and chronic lung injuries induced by infections and COPD are characterized by inflammatory responses, alveolar destruction, vascular remodeling, and scar tissue formation. These conditions impair the ability of the lungs to heal and regenerate under physiological conditions, ultimately leading to irreversible lung damage.[127–129] Mesenchymal stem cell-derived NPs (MSC-NPs), a well-established therapeutic modality in regenerative medicine, provide a robust foundation for research on lung tissue regeneration. This phenomenon is attributable, at least in part, to the posttranscriptional regulation of target genes by microRNAs (miRNAs).[130,131] For instance, exosomal microRNA miR-135a derived from human amniotic membrane MSCs has been demonstrated to enhance wound healing and stimulate fibroblast migration through the downregulation of large tumor suppressor kinase 2 expression.[132] In a mouse model of acute lung injury, keratinocyte growth factor (KGF) mRNA is essential for the therapeutic efficacy of EVs in treating lung pathology. KGF, a paracrine factor secreted by MSCs, was previously found to restore *E. coli* endotoxin and bacterium-induced acute lung injury (ALI) in isolated perfused human lungs. The therapeutic effect of such ENPs obtained by serum starvation is comparable to that of MSCs per se, although the likely mechanism involves the transfer of KGF mRNA to the injured alveolar epithelium and subsequent expression of the protein. This high-purity, low-volume formulation, which exhibits superior stability, has the potential to expand the scope of MSC-related regenerative therapies.[133]

To address the objective of alveolar regeneration in COPD, Tomomi Akita et al utilized the SS-cleavable proton-activated lipid-like material O-Phentyl-P4C2COATSOME®SS-OP, thereby ensuring the efficient delivery of Am80 (tamibarotene) to retinoic acid receptors within the nucleus of the cell. The encapsulation of Am80 within SS-OP ENPs facilitates its delivery into the cell nucleus following its release from the ENPs via ApoE and endosomes. This process underscores the capacity of ENPs for alveolar regeneration applications.[134] In the future, a broader range of engineered delivery systems and therapeutic agents is expected to be incorporated into strategies for promoting lung injury repair and regeneration. Insights can be extensively derived from regenerative studies in other organs and systems —such as the comparatively well-characterised repair processes of the liver, nervous tissue, and bone. While specific technical requirements may differ across these contexts, the underlying methodological frameworks and conceptual paradigms of regenerative medicine remain largely congruent.[135,136] Fatima Rizvi developed a biocompatible, non-integrative, and high-efficiency strategy for inducing transient expression of hepatocyte growth factor (HGF) and epidermal growth factor (EGF) in hepatocytes. This was achieved through the delivery of nucleoside-modified mRNA encapsulated within lipid nanoparticles (mRNA-LNPs) in a murine model, enabling targeted and temporary protein expression while avoiding the risks associated with genomic integration.[137] It is evident that analogous engineering strategies have previously been extensively implemented in other respiratory diseases, and it is anticipated that these aforementioned strategies will demonstrate enhanced efficacy in the domain of lung regenerative medicine.

Given the limited capacity of the lungs for regeneration and the disordered environment resulting from edema, inflammation, and fibrosis following alveolar rupture, the utilization of engineered ENP-based biological scaffolds has emerged as a pioneering strategy in the field of lung tissue engineering.[138] Hydrogel-based bioactive substance delivery devices represent a prevalent engineering modification strategy. Hydrogels possess inherent viscosity and elasticity that can be induced through chemical or physical cross-linking processes, which employ cross-linking agents. Such hydrogels are engineered to offer both structural and physical support, effectively replicating the cellular microenvironment. A pivotal feature of these materials is their ability to promote the regeneration of the lung's extracellular matrix (ECM), which serves as a critical structural scaffold. The ECM not only provides structural integrity but also regulates cellular growth, differentiation, and the dynamic interactions between cells and the matrix, thereby creating an optimal environment for lung cell proliferation and development.[139] These hydrogels have the potential to regulate the sustained release of molecules, thereby ensuring optimal efficacy while concomitantly minimizing adverse effects.[140] Zhu et al isolated decellularized extracellular matrix (dECM) from porcine lung tissue via a decontamination protocol, the purpose

of which was to remove cellular debris. The result of this process was the generation of lung dECM hydrogels. The utilization of the lung dECM hydrogel as a cell culture material had no effect on cell viability or cell growth, thereby signifying the satisfactory cytocompatibility of the structure, mechanical properties and degradation characteristics of the lung dECM hydrogel. The results indicated that through the downregulation of Ficolin signaling, lung dECM hydrogel administration attenuated bleomycin (BLM)-induced lung injury and fibrosis by suppressing M2 macrophage polarization. Thus, dECM hydrogels represent a promising class of biological materials for use in regenerative medicine.[141]

Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF), cystic fibrosis, and other respiratory diseases marked by pulmonary fibrosis result in chronic, progressive scarring of the lung parenchyma, ultimately leading to an irreversible decline in lung function. However, current antibiotic therapy may lead to drug resistance, whereas conventional drug delivery systems face the challenges of nonspecific modality distribution, poor drug absorption, destruction and elimination. Supportive care, which has been tentatively considered effective in the past, has difficulty reversing the process of pulmonary fibrosis.[142,143] Through the intrapulmonary route of administration, ENPs with smaller dimensions reduce the spatial site-blocking effects of the mucus network in fibrotic lung tissue and are more effective against infections accompanying pulmonary fibrosis. In addition, alterations in physical properties can help enhance the penetration of ENPs.[144] Dawson et al showed that neutrally charged polystyrene particles with diameters smaller than 200 nm exhibit faster transit through sputum compared to their charged counterparts.[145] Suk et al further illustrated that particles up to 200 nm in diameter, densely coated with low-molecular-weight PEG, penetrated sputum up to 90 times more rapidly than uncoated particles of comparable size.[146] This strategy facilitates the augmentation of drug delivery strategies via the lungs, circumventing the issues associated with elevated biological clearance and non-organ–specific distribution of oral as well as injectable drug delivery. These measures have been shown to increase the delivery efficiency of various carriers while preventing rapid clearance of the carriers from the respiratory tract.

Notwithstanding the distinctive benefits inherent to intrapulmonary drug delivery, the enhancement of the bioavailability of preexisting oral medications remains a subject that merits further investigation. Nintedanib (NIN) and pirfenidone are the only drugs approved for the treatment of IPF, and collaboration with synthetically engineered nanovesicles further endows these drugs with promise for application.[147] Rajwinder Kaur et al developed a solid lipid nanoparticle (NIN-SLN) to increase the bioavailability and decrease the hepatic and gastrointestinal toxicity of NIN. The results demonstrated that NIN-SLN significantly increased the NIN concentration in lung tissue and improved lung function indices in comparison with free NIN while minimizing side effects. Both quasistatic compliance (Cst) and inspiratory capacity (IC) in the NIN-SLN-treated groups were significantly increased, reflecting improvements in total lung capacity and lung stiffness. Furthermore, NIN-SLN significantly attenuated bleomycin-induced pulmonary fibrosis by inhibiting EMT, extracellular matrix remodeling and collagen deposition.[148] This increase in drug accumulation in target tissues subsequently led to a reduction in nonspecific effects, such as toxicity to other tissues.[149,150]

The efficacy of intrapulmonary drug delivery is hindered by poor drug permeability and drug retention in the airways due to collagen deposition in the mesenchyme during disease progression.[151] In light of the alterations and proliferation of mesenchymal tissues observed in pulmonary fibrosis, a key objective of developing modified ENPs has been to increase their drug penetration capacity and thus increase the drug concentration at the lesion site,[152] thereby optimizing therapeutic outcomes. In a seminal study, Bo Pan et al developed a novel class of ENPs that exhibited high permeation capacity. This objective was achieved by combining luteolin (LUT)-loaded hyaluronidase nanoparticles (Lut@HAase) with NHS-PEG1000-NHS as a cross-linking agent, and the resulting particles were characterized by their small size, stability, and suitability for noninvasive inhalation and accumulation in the lungs. Hyaluronidase at the lesion site can effectively degrade hyaluronic acid in mesenchymal tissues for effective penetration of LUT, thus exhibiting antioxidant, anti-inflammatory, antifibrotic, and antiapoptotic properties.[153]

ARDS

According to the Berlin definition, ARDS is a clinical syndrome characterized by acute onset, bilateral pulmonary infiltration evident on imaging studies, and persistent hypoxemia. ARDS is often induced by pneumonia and sepsis and

has a high mortality rate of approximately 40%. The COVID-19 pandemic has further exacerbated this situation. Traditional treatment modalities, including respiratory support and fluid management, often have difficulty preventing the progression of ARDS because of the complexity of the disease.[3,154] However, advancements in engineered NPs offer novel opportunities for the development of therapeutic agents.

Macrophages play an important role in the progression of ARDS-associated inflammatory responses. Therefore, targeting macrophages by nanoengineering anti-inflammatory drugs such as glucocorticoids is considered an effective strategy.[155] Xiong Liu et al explored the therapeutic potential of natural glycyrrhiza protein nanoparticles (GNPs) loaded with dexamethasone (named Dex@GNPs). Dex@GNPs are selectively taken up by neutrophils with the complement opsonization and then induce their apoptosis. The efferocytosis of apoptotic neutrophils by macrophages not only induces their polarization toward the M2 anti-inflammatory phenotype but also enhances the transfer of Dex\@GNPs, thereby facilitating the therapeutic effects of Dex. This strategy minimizes the toxicity associated with prolonged retention of the carrier and drug within the body.[156] Hua Jin et al developed naringin (Nar)-loaded PLGA NPs modified with a bone marrow derived-mesenchymal stem cell (BMSC) membrane (named CM@Nar-NPs). This engineered treatment is based on the fact that cell membrane coverage can help materials escape immune elimination. Experimental data indicate that CM@Nar-NPs achieve sustained drug release, improve biosafety, and specifically target the mitochondria of macrophages. The most significant impact of CM@Nar-NPs in mitigating cytokine storms is achieved through the efficient scavenging of ROS.[157] In addition, some studies have concentrated on identifying suitable nanomaterials for the delivery of siRNAs, which can silence genes implicated in the inflammatory response.[158]

Furthermore, targeted removal of relevant inflammatory mediators is also an effective treatment strategy. ROS has been shown to induce the gene expression of inflammatory mediators such as TNF-α and directly damage the airway epithelium.[159] Li et al designed a nanomaterial named TPCD using β-CD as the basic scaffold and coupling Tempol (Tpl) with phenylboronic acid pinanolide ester (PBAP). The combination of the two antioxidants enabled the system to exhibit broad-spectrum ROS clearance ability. And TPCD has ROS-dependent hydrolytic properties. In the presence of H2O2, TPCD NPs can rapidly hydrolyze within a short period of time and release the Tempol and PBAP units. This property helps its targeted release at inflammatory or injured sites, reducing side effects in normal tissues.[160] The neutrophil elastase (NE) released by polymorphonuclear neutrophils (PMN) can also serve as a response strategy. By embedding NE-specific protease-sensitive peptides into nanoparticles, it is possible to rapidly release the encapsulated targeted drugs such as Nexinhib20 in the pulmonary inflammatory environment with high NE concentration, which can inhibit the NE release process. However, this approach still cannot address the drawback of the nanoparticles themselves increasing inflammatory indicators and reducing appropriate immune responses.[161]

Pulmonary edema secondary to ARDS compromises epithelial cell integrity by diminishing surfactant levels. Research indicates that mechanical ventilation exacerbates this condition, which can lead to ventilator-induced lung injury (VILI) and contribute to increased patient mortality. There is an urgent need to explore novel strategies to address this critical issue.[162] The use of engineered LNPs for mRNA delivery has emerged as an effective option. Traditional cationic LPNs (cLNPs) can be modified by selective organ-targeting molecules to form specific protein coronas, thereby fulfilling the requirements of tissue targeting.[163] Specifically, cLNPs modified with particular serum proteins can be designed for identification by a series of receptors, including scavenger receptors and integrins, on the surface of the lung endothelium. Moreover, mRNAs can express challenging proteins without the need to enter the nucleus. Leveraging these advantages, Katrin Radloff et al constructed the mRNA-76-cLNP complex to target the Ang/Tie-2 receptor tyrosine kinase signaling pathway. This complex exhibited significant efficacy in reducing pulmonary edema and demonstrated high spatial confinement in a mouse model of IPML.[164]

Perspectives and Current Challenges

Current engineering strategies for NPs are predominantly focused on enhancing lung-targeted precision and multidrug encapsulation efficiency for optimized delivery efficacy and combination therapies.[165–167] These advancements are expected to address clinical challenges such as drug resistance, inflammatory dysregulation, and immune imbalance. Nevertheless, current understanding of ENP formulations and their mechanisms, including interactions with pulmonary

microenvironments and long-term biocompatibility, remains in the early stage. Several challenges must be addressed to bridge the gap between preclinical and clinical studies.

Heterogeneity

Large-scale application is based on the assumption of homogeneity in critical parameters such as size, charge, composition, and density, all of which directly govern the physicochemical properties of NPs. However, technical limitations, such as material purity, formulation processes and postproduction stability, often introduce variability in batches, subpopulations and even individual particles.[168–171] While microfluidic-based production platforms enhance reproducibility and control over NP size and dispersity, they remain limited by nonuniform solvent and component mixing due to droplet diffusion and pairing inconsistencies, leading to residual heterogeneity.[172] Such variability could impact therapeutic outcomes and equivalent dosage calculations. For example, the liposomal distribution within tumors is influenced by zeta potential, membrane fluidity and size, which collectively determine the ability of liposomes to reach peripheral, intermediate, and central tumor regions.[173] Similarly, the lipid headgroup, tail length, and concentration affect the efficiency of liposome internalization in triple-negative breast cancer cells.[174]

With respect to NP functionalization, cargo accumulation and surface ligand modification also contribute to inhomogeneity. Zuriñe Erana-Perez et al constructed engineered EVs derived from C2C12 myoblasts overexpressing erythropoietin (EPO), with large EV groups demonstrating nearly 100-fold more EPO protein and 8-fold greater mRNA loading capacity than small EV groups.[175] Points accumulation for imaging in nanoscale topography (PAINT) has revealed stark differences in DNA strand distribution and quantity among individual particles.[176] Single-particle analysis of polymeric poly(lactide-*co*-glycolide)-poly(ethylene glycol) (PLGA–PEG)-conjugated NPs revealed a correlation between particle size and ligand density. Notably, the presence of ligand-deficient subpopulations may result in a 5-fold overestimation of ligand availability, highlighting risks in therapeutic dosing.[177] In addition, advances in antibody modification, such as optimized orientation, density, and site-specific conjugation, have improved the precision of cell targeting in comparison with conventional methods.[178–180] For engineered EVs, variations in surface ligands and intraparticle payloads are rarely characterized.[181,182]

To date, NP heterogeneity has seldom been addressed in clinical trials. Comprehensive characterization at the single-particle level and the use of multiparametric techniques are essential to ensure controlled drug delivery and efficacy.[177,181,183] Furthermore, the impact of NP variability on therapeutic outcomes in pulmonary diseases requires further exploration.

Administration

Nanomedicine administration via the pulmonary route, or inhalation delivery, remains a cornerstone in respiratory therapeutics. This approach offers distinct advantages, including localized drug accumulation in targeted lung tissues, enhanced therapeutic efficacy, and reduced systemic toxicity.[184,185] Polymeric nanocarriers, such as biodegradable PLGA and chitosan-based dry powder inhalers (DPIs), leverage aerodynamic properties to achieve deep lung deposition while minimizing off-target effects.[186] Lipid NPs have demonstrated efficient mRNA delivery to lung cells for vaccines against SARS-CoV-2 and metastatic lung cancer, although physiological and mechanical barriers exist. High shear forces during nebulization compromise particle integrity and cargo stability, and mucosal clearance impedes epithelial targeting, whereas inefficient endosomal escape mechanisms limit mRNA bioavailability. Kim et al identified an NP formulation with β-sitosterol and high PEG lipid contents that exhibited postnebulization stability and effective intracellular mRNA transfection.[187] Notably, inhalable and biocompatible EVs have become another promising RNA delivery platform, yet relevant research is still in its infancy.[188,189]

Nevertheless, the issue of biocompatibility requires further investigation for clinical usage. While inorganic nanoparticles exhibit desirable uniformity and antimicrobial properties, several studies have indicated that inhalation exposure to silver NPs may cause lung toxicity and cardiovascular impairment.[190] Surface modifications, such as PEGylation, may alter mucociliary clearance dynamics. Although several in vitro studies have reported minimal toxic effects of inhalable polymeric microparticle carriers,[191,192] comprehensive evaluation of their pulmonary exposure, particularly regarding long-term exposure durations, is limited. Characterization of biocompatibility remains necessary owing to the

predominant application of these sustained-release systems in managing chronic respiratory diseases, which require repeated administration. However, current preclinical assessments predominantly rely on acute exposure models (≤14 days), whereas clinical treatment protocols typically involve multi-month therapeutic regimens. Toxicology examinations should focus on the immune response and remodeling of the pulmonary microenvironment. In addition, chronic pulmonary inflammation exacerbates epithelial barrier dysfunction, potentially resulting in extrapulmonary distribution.[184] Furthermore, there is still a lack of understanding regarding the relationships of the physicochemical properties of NPs (size, shape and surface charge) with their in vivo fate and interactions with pulmonary surfactants. Therefore, a clinically viable and biocompatible NP formulation for safe and effective pulmonary drug delivery remains a formidable and ongoing challenge.

Translation from Bench to Bedside

Various engineered nanoparticles have demonstrated promising capabilities for gene regulation, tumor targeting and regeneration in preclinical studies. While preclinical data are promising, clinical translation remains low (<15% success from animal models to human clinical trials), with a significant attrition rate in early-phase clinical trials. According to a survey based on cancer nanomedicine, the success rates in Phase 2 and 3 trials were 48% and 14%, respectively, primarily due to inadequate therapeutic efficacy.[193] Similarly, several studies have reported failed EPR effect, different accumulation (5–33%) and size distribution of nanoparticles in tumor sites according to different tumor types.[194,195] Discontinuation of Centers of Cancer Nanotechnology Excellence (CCNEs) program underscored the severity of attrition: despite large investments, most candidate formulations did not progress to approval, and those tested rarely demonstrated improved efficacy over free drugs when rigorously compared (for example, BIND-014 in Phase 1 and NK-105 in Phase 3).[193,196,197] Liposomal amikacin for inhalation (LAI) for nontuberculous mycobacterial lung infectious disease entered late-phase clinical trials. However, documented treatment-emergent adverse events (TEAEs) reached 88%-90%, with the incidence rates of severe TEAEs (including bronchiectasis exacerbation, pneumonia and dyspnea) reaching 15%, potentially limited its broader clinical adoption.[198,199] Clinical reports and trial registries document both positive microbiologic endpoints and safety signals (higher frequency of respiratory TEAEs) in LAI trials. MSC-derived EVs have strong preclinical efficacy for ARDS and pneumonia, but still remain at an early clinical stage. A few multicenter Phase 3 investigations, such as ExoFlo (IV EV preparations for ARDS, NCT05354141), are now registered. Regrettably, due to the lack of preclinical studies on ExoFlo, the exact efficacy remains to be discussed. Phase 3 efficacy outcomes in ARDS or other severe respiratory diseases have rarely been reported. Thus, while EVs hold great promise, clinical efficacy remains to be validated in adequately randomized trials.[200]

These findings indicate that NPs are often not more effective than ideal preclinical studies, largely because of an insufficient understanding of in vivo biological interactions, including targeted delivery, pharmacokinetics, cellular internalization mechanisms, and intracellular trafficking pathways. Future work must address species differences and scalable manufacturing. Limitations of current preclinical models hinder accurate prediction of human responses. While murine models dominate respiratory research, fundamental interspecies differences in lung physiology, immune responses and disease pathology, as well as genetic diversity and environmental exposure, often lead to discrepancies in therapeutic outcomes.[201] For example, ENPs optimized for rodent alveolar macrophages may fail to account for human-specific cellular uptake mechanisms. Advanced models, such as human lung organoids or ex vivo precision-cut lung slices, provide novel perspectives for investigating respiratory pathologies and nanoparticle interactions but require standardization to improve translational efficacy.[202,203] Patient-derived tumor explant models (PDX), which incorporates animal models with patient-derived cells, may achieve closer similarity to the human pathological microenvironment.[195]

Scalability and reproducibility have also become major obstacles to be considered in bench-to-bedside translation. Additionally, complex NP formulations may suffer from batch-to-batch variability during large-scale synthesis.[204] This inconsistency potentially impacts colloidal stability, drug-loading efficiency and biodistribution profiles. Industrial-scale manufacturing must address cost-effectiveness while maintaining stringent quality control, especially for inhaled NPs, which require precise aerodynamic particle sizes (1–5 μm) to ensure optimal lung deposition and aerosol performance.[79] Improved process control technologies, such as microfluidics and flash nanoprecipitation (FNP), have shown great promise in scalable production.[205] Reproducibility challenges extend to preclinical studies. Variations in experimental

protocols, such as dosing regimens, nanoparticle characterization methods, and disease induction techniques, contribute to conflicting results across laboratories. Standardized guidelines for ENP characterization (eg, ISO/TS 21362) and disease-specific evaluation frameworks are urgently needed to harmonize research outcomes.[206]

Significant regulatory challenges impede the development and approval pathway for nanomedicines. The complex pharmacokinetics and pharmacodynamics exhibited by NPs, arising from their multi-component and multifunctional structure, fundamentally differ from those of bulk materials. As current regulations are established for conventional formulations, a knowledge gap persists regarding the translation of NP physicochemical properties to predictable in vivo outcomes, such as aerosolization, deposition in different regions of the lung, and stability under physiological airflow conditions. This gap critically limits the utility of existing safety and toxicological assessment frameworks for evaluating nanoformulations.[207] Furthermore, the classification of nanomedicines varies across jurisdictions. A product may be defined as a biological agent in one country but as a medical device in another, resulting in inconsistent regulatory pathways.[208]

The emerging discipline of nanomedicine has a bright future, but the different policies and strategies adopted by various countries regarding its development have led to significant disparities in the corresponding research achievements at present. The developed countries led by the United States recognized the value of nanotechnology in the biomedical field relatively early. A typical example is that the National Cancer Institute (NCI) has been investing a large amount of money in this field every year and establishing relevant technology programs since the early 21st century.[209] Thanks to this, the current nanomedicine market in Western countries has established a relatively complete approval and listing system, and the corresponding safety issues of nanomaterials have been strictly regulated by institutions such as the FDA. In comparison with it, developing countries such as China lack relevant governance and regulatory experience.[208] It is worth noting that in recent years, the Chinese government has provided considerable policy and financial support to the field of nanomedicine. By fostering collaboration between research institutions and universities, the international recognition of this field in China has been rapidly increasing. In addition, the traditional Chinese herbal medicine in its culture has also become a major feature in its nanotechnology research.[210] However, the drawback of a late start has led to the fact that most of the current nanotechnology research in China cannot be translated into clinical practice. Although a large number of related papers have been published, their citation rates are far lower than those of the United States, Germany and other countries.[211] Therefore, in order to achieve innovative breakthroughs in this field, international cooperation is indispensable. These collaborations enable Chinese researchers to access advanced technologies and clinical trial frameworks, which helps to narrow the gap between research and clinical application.

In conclusion, to bridge the current translation gap, future research should prioritize two strategies: 1) enhancing nanoparticle specificity and therapeutic potency through further understanding of biological interactions; 2) simplifying formulation designs to facilitate scalable manufacturing without influencing functionality.

Conclusion

NPs represent promising advancements in the domain of nanomedicine and the treatment of respiratory diseases. For example, in lung cancer, the EPR effect of NPs improves tumor-specific efficacy and minimizes chemotherapeutic systemic toxicity. Likewise, in pulmonary infections, inhaled NPs deliver antibiotics directly to the site of infection, overcoming the challenges of lung's biological barriers and multidrug-resistant pathogens. The engineering strategies used to develop ENPs contribute to enhancing the therapeutic efficacy by improving their biocompatibility, bioavailability, targeting, and tissue penetration. The lack of standardized manufacturing processes and limited clinical trial data are the foremost obstacles that must be addressed. Issues related to biocompatibility, stability, and long-term safety of ENPs need further investigation. Large-scale production and clinical application require regulatory approval.

In conclusion, ENPs hold immense potential in revolutionizing the treatment of respiratory diseases by providing more targeted and effective therapies. It is crucial to further understand the biological interactions of ENPs, prioritize the uniformed formulations and actionable production standards, conduct rigorous clinical trials, and improve regulatory frameworks. These "science-clinic-market" steps will ensure that ENPs can be successfully translated from laboratory research to routine clinical applications, ultimately enhancing the treatment of patients with respiratory diseases and paving the way for more personalized and effective therapies in the future.

Data Sharing Statement

The data presented in this study are available on request from the corresponding authors.

Author Contributions

Conceptualization, L.Z. and D.L.Y.; writing—original draft preparation, B.Q.C. and Y.H.L.; supervision, Y.L.W. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflict of interest.

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