

# Targeting Multiple Pathophysiological Axes in COPD: Nanomaterial Advances

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**Abstract:** Chronic obstructive pulmonary disease (COPD), a leading global cause of mortality and morbidity, imposes substantial socioeconomic burdens due to its progressive nature and limited therapeutic efficacy. Current strategies face dual challenges: suboptimal pulmonary bioavailability of pharmacologic agents and systemic toxicity from non-targeted drug distribution. To address these limitations, this review establishes a mechanistic framework through the first systematic identification of COPD-specific nano-intervention targets, organized around four core pathophysiological axes: (1) dysregulated inflammatory cascades, (2) redox imbalance mechanisms, (3) protease-antiprotease homeostasis disruption, and (4) progressive airway remodeling. We critically evaluate respiratory-adaptive nanocarrier systems, including polymer nanoparticles (PLGA-PEG) with 6.5-fold enhanced Neutrophil targeting efficiency ( $*p < 0.001$ ) and lipid nanoparticles (LNPs) achieving >90% siRNA-mediated inflammatory gene suppression. Despite advancements, clinical translation remains hindered by technical limitations in nanoparticle engineering, chronic pulmonary biocompatibility risks (eg, silica nanoparticles elevating TGF- $\beta$  by 1.8-fold,  $*p < 0.05$ ), and stringent regulatory requirements. Future research must prioritize intelligent stimulus-responsive platforms for inflammation-triggered drug release, multidisease targeting nanotechnologies, and AI-driven patient-specific formulations. By integrating mechanistic insights with translational strategies, this work provides a roadmap to advance nano-interventions toward precision therapeutics for COPD.

**Keywords:** COPD, nanomaterial, drug delivery, targeted therapy, nanocarriers

## Introduction

COPD ranks among the top three causes of global mortality, responsible for 3.5 million deaths in 2021 (5% of total deaths) and imposing a significant socioeconomic burden.<sup>1,2</sup> COPD is a heterogeneous inflammatory disorder characterized by persistent Airway and parenchymal inflammation. The pathophysiological triad of chronic airflow limitation, recurrent acute exacerbations, and multisystemic inflammation underpins COPD progression, with impaired mucociliary clearance mechanisms synergizing with mucous hypersecretion to compromise therapeutic efficacy through reduced pulmonary drug retention and suboptimal bioavailability.<sup>3,4</sup> This self-perpetuating cycle of airway obstruction (manifested clinically as dyspnea, productive cough, and bronchial hyperresponsiveness) coupled with the socioeconomic Burden of disease management necessitates innovative therapeutic paradigms.<sup>5</sup> Nanoscale delivery systems demonstrate particular promise in respiratory medicine, leveraging engineered physicochemical properties to enhance sputum penetration, prolong mucosal adhesion, and achieve targeted cellular uptake—capabilities that overcome traditional limitations of conventional pharmacotherapy.<sup>6,7</sup> In the field of COPD treatment, nanomaterials can be used as drug delivery systems to realize precise

targeted drug delivery, and can also act as gene carriers to provide strong support for gene therapy; at the same time, their use in COPD biomarker detection can play a key role in early diagnosis and monitoring of the condition.<sup>8–15</sup> In the treatment of COPD, traditional pharmacological and non-pharmacological therapies still occupy an important position. However, in view of its complex pathogenesis and diverse therapeutic targets, nanomaterials provide a new strategy to break through the existing therapeutic bottlenecks.<sup>16,17</sup> Its function is twofold: firstly, to improve the concentration of drugs reaching the local area, and secondly, to enhance the solubility and diffusion of the drug. The result of these processes is an increase in the bioavailability of the drug.<sup>18</sup> The employment of nanomaterials in the treatment of COPD confers a distinct advantage, substantially enhancing the therapeutic efficacy of the intervention and mitigating the disease burden. The multifaceted pathogenesis of COPD necessitates the employment of nanomaterials as a means to enhance the therapeutic effect of COPD by targeting specific COPD targets.<sup>19</sup> Although the potential of nanomaterials in the treatment of COPD has gradually emerged, the clinical application of nanomaterials in the treatment of COPD still faces multiple challenges. Specifically, the safety of nanomaterials is the primary concern, and their potential inflammatory response, cytotoxicity, and potential carcinogenicity under long-term exposure need to be highly emphasized in their design and application.<sup>20–22</sup> Stability is also a key bottleneck, and although surface modification technology has improved this problem to some extent, its impact on biocompatibility and drug delivery efficiency still needs to be evaluated in depth.<sup>23</sup> In addition, high production costs, complex preparation processes, stringent quality control requirements, and the lack of uniform regulatory guidelines and standardization systems have combined to constrain the clinical translation of nanomaterials, so the establishment of a comprehensive regulatory framework and standardized processes to safeguard their safety and efficacy has become an urgent issue.<sup>24–28</sup> No previous review has systematically reported the therapeutic targets of nanomaterials. Through an extensive review of domestic and international literature, this review systematically summarizes and analyzes the research on the targets of nanomaterials in COPD therapy to fill this gap, which is of key significance in promoting the development of disease therapeutic solutions. This review focuses on the possible targets of nanomaterials in COPD and summarizes nanomaterials used in COPD.

## Inflammation-Related Targets

COPD is pathologically sustained by dysregulated inflammation, stemming from pathological crosstalk between immune cells and inflammatory mediators. Central to this process, the pulmonary inflammatory landscape integrates innate and adaptive immunity through a self-amplifying network of cellular and molecular interactions that exacerbate inflammatory cascades and maladaptive immune activation.<sup>29</sup> Below, we dissect these inflammatory hubs and their targeting by nanomaterials,<sup>30</sup> with cell-specific nanointervention strategies systematically cataloged in [Table 1](#).

## Inflammatory Cells

### Alveolar Macrophages

Alveolar macrophages are an important component of the innate immune system and play a key role in chronic inflammation in COPD through their phagocytic and immunomodulatory functions, and positively correlate with the severity of the disease.<sup>44</sup> Studies have demonstrated that the number of alveolar macrophages in COPD patients is markedly elevated, showing a 5- to 10-fold increase compared to healthy controls.<sup>45–47</sup> Furthermore, smokers exhibit significantly increased interstitial macrophage (IM) accumulation within alveolar septa, with total IM numbers and local density elevated by 36% ( $p < 0.01$ ) and 56% ( $p < 0.001$ ), respectively, relative to nonsmokers.<sup>48</sup> However, prolonged exposure to harmful substances, such as cigarette smoke, can lead these cells to trigger abnormal inflammatory responses and cause dysfunctional phagocytosis.<sup>30</sup> Aggregated macrophages secrete a variety of inflammatory mediators, including lipid mediators (eg, leukotrienes, prostaglandins), chemokines (eg, IL-8, IP-10), inflammatory cytokines (eg, TNF- $\alpha$ ), growth factors (eg, TGF- $\beta$ , TGF- $\alpha$ ), as well as leukotriene B4 (LTB4) and reactive oxygen species (ROS), which, in varying degrees, influence the COPD inflammatory response, making alveolar macrophages an important target for COPD treatment.<sup>49,50</sup> Nanomaterials are used to design targeted drug delivery systems for anti-inflammatory drug delivery by virtue of their unique physicochemical properties - such as tunable size for passive targeting across physiological barriers and surface modifiability for active ligand-mediated recognition. These nanocarriers significantly enhanced drug uptake by alveolar macrophages and inhibited the release of key pro-inflammatory cytokines, thereby alleviating inflammation in COPD.<sup>51,52</sup>

**Table I** The Comparison of Different Nanoparticle Therapies

Target Cell	Types of Nanoparticles	Function	Action
Alveolar macrophages (AMs)	Mannose-Modified Lipid-Polymer Hybrid Nanoparticles (Man-LPHFNPs) <sup>31</sup>	Enhance drug targeting and uptake Inhibit inflammatory mediators Attenuate pulmonary inflammation in COPD models	Mannose modification enhances drug targeting and uptake by macrophages; delivered roflumilast inhibits PDE4 and related signaling pathways to reduce inflammatory mediators and exert anti-inflammation.
	Dipalmitoylphosphatidylcholine (DPPC) liposomes with mannose-ligand delivering bergamottin <sup>32</sup>	Enhance cellular uptake Activate anti-inflammatory pathways and Inhibit pro-inflammatory signals Promote macrophage phenotype conversion Attenuate lung inflammation in acute lung injury models Reduce inflammatory mediators	Mannose ligand binds to AMs' CD206 receptors to boost uptake; bergamottin activates PPAR $\gamma$ , inhibits NF- $\kappa$ B, and promotes M1-to-M2 macrophage polarization for anti-inflammation and tissue repair.
	Gold nanoparticles (AuNPs) coated with hexapeptide (P12) <sup>33</sup>	Promote macrophage polarization Improve repair of LPS-induced lung injury in mice Provide a novel paradigm for targeted immunotherapy of AMs	Targets AMs via their phagocytic properties; promotes macrophage polarization to anti-inflammatory phenotype, aiding lung injury repair.
Neutrophils	PLGA-PEG NPs modified with NIMP-R14 antibody (PINP) delivering ibuprofen <sup>34</sup>	Deliver drugs (eg, ibuprofen) to neutrophils, reduce lung inflammation in Pa-LPS and cigarette smoke-induced models, showing potential in COPD treatment.	NIMP-R14 antibody enables specific recognition of neutrophils, facilitating targeted drug delivery.
	Nanoparticles with surface-aggregated complement proteins (eg, C3 and C5) <sup>35</sup>	Precisely deliver therapeutic agents to damaged lungs, attenuate lung inflammation in COPD models, with fewer systemic side effects.	Complement proteins promote nanoparticle-neutrophil binding, enabling effective migration to inflammation sites.
Eosinophils	R321 (peptide molecule with PEG and aspartic acid modifications) <sup>36</sup>	Blocks CCR3-mediated eosinophil chemotactic recruitment and airway hyperresponsiveness, providing an innovative strategy for eosinophil-targeted therapy in COPD.	Mimics CCR3's transmembrane domain (TM2) to bind CCR3, inhibits G protein signaling via "biased mechanism", and promotes receptor degradation.
	Zinc oxide nanoparticles (ZnO) <sup>37</sup>	Targets eosinophils, delays human eosinophil apoptosis, and influences COPD-associated inflammatory responses by regulating pro-inflammatory cytokine production.	Inhibits caspase activity, blocks degradation of caspase-4 and Bcl-xL, and elevates IL-1 $\beta$ and IL-8 production.
	Reactive oxygen species-responsive nanoparticles (NPs-FDTN) <sup>38</sup>	Delivers Fedratinib to eosinophil-enriched lung microenvironment, induces eosinophil apoptosis, reduces airway eosinophil infiltration.	Surface-modified Fc fragment binds lung epithelial FcRn, crosses barrier via cytophagy; releases Fedratinib under ROS stimulation, blocking JAK2/STAT5 pathway in eosinophils.
"Dendritic cells	Functionalized gold nanoparticles (AuNPs, mediated through DC-SIGN receptors) <sup>39</sup>	Specifically target monocyte-derived dendritic cells (MDDCs), upregulate MHC-II expression to activate cellular immune functions, and remodel immune response homeostasis.	Mediated by DC-SIGN receptors for specific targeting; upregulate MHC-II to activate immune functions.
	Multifunctional gelatin nanoparticles (Dex-NPs, surface-modified by gold/silver alloy nanoclusters, loaded with OVA antigens) <sup>40</sup>	Be specifically taken up by DCs, upregulate MHC-II and co-stimulatory molecules (CD86/CD80/CD40) expression, enhance antigen presentation, and promote specific immune responses.	Dextran functionalization enables DC targeting; synergistically deliver antigens and immunomodulators to upregulate key molecules.
	Broccoli-derived nanoparticles (BDN) <sup>41</sup>	Target DCs to inhibit overactivation, induce immune tolerance, block Gr1+monocytes differentiation to pro-inflammatory CD11b+ DCs, and attenuate inflammatory response.	Activate AMPK signaling pathway in DCs to maintain immune homeostasis.
T cells	Plant-derived nanovesicles (Asteryomena callus-derived) <sup>42</sup>	Target T cells and their microenvironment, inhibit proliferation/activation of CD4+ and CD8+ T cells, reduce pro-inflammatory cytokine release, and may attenuate inflammatory response in COPD by modulating T-cell behavior.	Load immunomodulatory nucleic acids, proteins or small molecules; inhibit T-cell over-activation (via affecting dendritic cell function); alter cytokine microenvironment (reduce Th2/pro-inflammatory cytokines, promote IL-10).
B lymphocytes	Anti-CD20-modified NPs (antibody-decorated) <sup>43</sup>	Deliver drugs directly to B cells, reduce inflammatory mediators (eg, TNF, IL) secreted by B cells, and alleviate COPD-related inflammatory response.	Bind to CD20 antigen on B cells for specific targeting, enabling direct drug delivery to B cells.

For example, mannose-modified lipid-polymer hybrid nanoparticles (Man-LPHFNPs) can deliver roflumilast targeted to alveolar macrophages. Such hybrid nanomaterials, on the one hand, improve the targeting and uptake efficiency of the drug in macrophages through mannose modification, and on the other hand, inhibit PDE4 through the delivered drug roflumilast, which in turn inhibits the related signaling pathways and reduces the production of inflammatory mediators, thus exerting anti-inflammatory effects. This study demonstrated that this targeted delivery system significantly attenuated the pulmonary inflammatory response in a COPD model, providing a new strategy for the treatment of chronic inflammation in COPD patients.<sup>31</sup> Similarly, for the key target of alveolar macrophages, another study utilized bergamottin combined with dipalmitoylphosphatidylcholine (DPPC) liposomes to develop a lung-targeting bioactive lipid nanomedicine for precise therapeutic intervention. The surface-modified mannose ligand specifically binds to CD206 receptors on alveolar macrophages, significantly enhancing cellular uptake efficiency. Concurrently, delivery of the natural active molecule bergamottin activates the PPAR $\gamma$  pathway, effectively inhibiting NF- $\kappa$ B inflammatory signaling and promoting macrophage polarization from pro-inflammatory M1-type to anti-inflammatory M2-type. The resulting M2-type macrophages secrete anti-inflammatory factors, suppress inflammatory responses, and promote tissue repair.<sup>32</sup> This nanomedicine significantly attenuated lung inflammation and reduced inflammatory mediator levels in an acute lung injury model. In a separate study, unique anti-inflammatory nanodrug, P12 (made of hexapeptides and gold nanoparticles), gold nanoparticles coated with a hexapeptide were designed to target alveolar macrophages via their phagocytic properties, similarly promoting macrophage polarization and improving repair of LPS-induced lung injury in mice.<sup>33,53</sup> This approach provides a novel paradigm for targeted immunotherapy of alveolar macrophages. Consequently, macrophage-targeting nanosystems represent a promising therapeutic strategy for COPD and other chronic airway diseases. These studies not only verified the effectiveness of nanomaterials in COPD treatment but also provided a theoretical basis for the development of novel nanomedicines. Future studies should further optimize the design of nanomaterials, improve their targeting and safety, and explore their potential for clinical applications.

## Neutrophils

Neutrophils are central to the pathogenesis of COPD, and airway neutrophils are increased in all patients with COPD, regardless of age of onset, clinical phenotype, or disease severity. As a key component of innate immune cells, a large body of data suggests that neutrophils play a key driving role in COPD airway inflammation, with their numbers strongly correlating with reduced FEV1, chronic sputum coughing, and degree of airway obstruction.<sup>49,54</sup> In patients with COPD, the release of neutrophil products (eg, proteases such as neutrophil elastase NE, protease 3 Pr3, and histone B CatB) was significantly elevated.<sup>55</sup> Among them, protein hydrolases stimulate mucus secretion and affect mucus cilia clearance function, while neutrophils can increase protease activity, leading to further tissue damage.<sup>54</sup> Hydrolytic enzymes such as elastase cause tissue damage by degrading the extracellular matrix, and after destroying the airway barrier function, more inflammatory mediators enter the lung tissues, which further produce chemokines and attract neutrophil infiltration, forming a vicious cycle.<sup>56</sup> Therefore, effective targeted delivery of drugs to neutrophils is essential to reduce the inflammatory response, and nanomaterials are significant in this regard. Experiments have been conducted to develop a neutrophil-targeted nanodrug delivery system (PINP) using PLGA-PEG nanoparticles modified with NIMP-R14 antibody to specifically recognize neutrophils. PINP effectively delivered drugs such as ibuprofen to neutrophils in a mouse model and significantly reduced lung inflammation in Pa-LPS and cigarette smoke-induced inflammation models, demonstrating its potential in the treatment of COPD.<sup>34</sup> In other experiments, by aggregating proteins on the surface of the nanoparticles to confer their tropism towards neutrophils, complement proteins (eg, C3 and C5) were utilized to promote nanoparticle-neutrophil binding for effective migration towards the site of inflammation, and to deliver the therapeutic agents to the damaged lungs precisely with fewer systemic side effects. Studies have shown that such nanoparticles significantly attenuate the inflammatory response of the lungs in COPD models, providing a new strategy for COPD treatment.<sup>35</sup> These studies validate the effectiveness of nanomaterials in COPD treatment and provide a theoretical basis for novel nanomedicine development. Future studies should further optimize the design of nanomaterials that can target cell surface receptors based on ligand-receptor specific interactions to improve targeting and safety, and explore their potential for clinical applications.

## Eosinophils

In COPD, eosinophils, as common inflammatory cells, are key cells in inflammation-driven and airway remodeling through the release of cytotoxic proteins and cytokines, which can both directly cause tissue damage and airway hyperresponsiveness and exacerbate inflammation and airway remodeling.<sup>57</sup> Clinically, blood and sputum eosinophil counts are used as biomarkers to guide individualized treatment, and targeted therapy for them has become one of the key entry points for COPD treatment.<sup>58</sup> Nanomaterials, as a research hotspot in recent years, have made some progress in targeting eosinophils. The effects of nanomaterials on eosinophils are manifold, involving apoptosis, cell signaling pathways, cell adhesion, and cytokine production, as well as influencing related cell signaling pathways that regulate inflammatory responses, all of which provide new directions for the development of therapeutic strategies targeting eosinophils in COPD disease.<sup>59,60</sup> For example, R321 is a novel peptide molecule designed based on the second transmembrane helix of CCR3 receptor, with 27 units of polyethylene glycol (PEG) and three aspartic acid residues modified at the C-terminus. CCR3 is a key chemokine receptor recruited by eosinophils, and R321 binds to the receptor by mimicking the transmembrane structural domain (TM2) of CCR3 and utilizing the “biased mechanism. By mimicking the binding of CCR3 transmembrane structural domain (TM2) to the receptor, R321 uses the “bias mechanism” to inhibit only the G protein signaling of CCR3 and promote the degradation of the related receptor, thus effectively blocking CCR3-mediated eosinophil chemotactic recruitment and airway hyperresponsiveness. By circumventing drug tolerance mechanisms, R321 has been demonstrated to provide an innovative strategy for eosinophil-targeted therapy in COPD.<sup>36</sup> When specifically targeting the CCR3 receptor pathway, nanomaterials mediate suppression of inflammatory cell infiltration and amelioration of airway hyperresponsiveness. In addition, it was found that zinc oxide nanoparticles (ZnO) could target eosinophils and delay the apoptotic process of human eosinophils. The mechanism of action includes inhibition of cysteine asparaginase (caspase) activity, blocking the degradation pathway of caspase-4 and Bcl-xL, and significantly elevating the production of the pro-inflammatory cytokines IL-1 $\beta$  and IL-8. This regulatory effect may influence the pathologic course of COPD-associated inflammatory responses. Importantly, experimental validation in this study demonstrated that human eosinophils could serve as a novel direct action target for ZnO nanoparticles.<sup>37</sup> In another asthma study, researchers constructed reactive oxygen species-responsive nanoparticles (NPs-FDTN) targeting FcRn. Its surface-modified Fc fragment was specifically delivered to the eosinophil-enriched inflammatory microenvironment of the lungs by binding to the FcRn receptor of lung epithelial cells and crossing the epithelial barrier via cytophagy. Under local ROS stimulation, the nanosystem releases encapsulated Fedratinib (FDTN), which directly induces eosinophil apoptosis in a concentration-dependent manner by precisely blocking the JAK2/STAT5 signaling pathway in eosinophils, thus effectively reducing the level of airway eosinophil infiltration and exerting therapeutic effects.<sup>38</sup> The interventional efficacy of nanoformulations on COPD pathological progression has been experimentally validated, with molecular-level mechanistic elucidation further providing theoretical foundations for novel drug development. Subsequent investigations should prioritize precise optimization of nanocarrier structure-function compatibility, focus on overcoming enhancement bottlenecks in biological targeting precision and in vivo safety thresholds, while concurrently advancing systematic validation of clinical translation potential.<sup>61–63</sup>

## Dendritic Cells

In COPD research, dendritic cells (DCs) have garnered extensive attention as critical mediators bridging innate and adaptive immunity.<sup>64</sup> Studies have demonstrated that DCs in the lung tissues of COPD patients persistently remain activated, with their activation levels shown to positively correlate with clinical disease stages. Within immune response regulatory networks, the activation of inflammatory effector cells such as neutrophils and Th17 cells has been identified to be mediated by these professional antigen-presenting cells enriched in airway-parenchymal regions, thereby exerting pivotal regulatory functions.<sup>65</sup> Based on these mechanisms, DC-targeted intervention strategies have been incorporated into the core technical framework of COPD prevention and treatment systems. To enhance disease management efficacy, novel therapeutic modalities focusing on DC functional regulation have been established as research priorities.<sup>66</sup> Functionalized gold nanoparticles (AuNPs) mediated through DC-SIGN receptors have been confirmed to specifically target monocyte-derived dendritic cells (MDDCs), where upregulation of MHC-II expression is employed to activate cellular immune functions, thereby achieving remodeling of immune response homeostasis. The development of

nanocarriers with lung DC-targeting capability and immunoregulatory properties has been supported by multidimensional evidence from this finding.<sup>39</sup> A study was conducted by developing multifunctional gelatin nanoparticles (Dex-NPs) whose surface was modified by gold/silver alloy nanoclusters and loaded with ovalbumen (OVA) antigens, while dendritic cell targeting was achieved through dextran functionalization. The nanosystems were specifically taken up by DCs and significantly upregulated the expression of MHC-II molecules and co-stimulatory molecules (CD86/CD80/CD40) on the surface of DCs by synergistically delivering antigens and immunomodulators, thereby enhancing antigen presentation and promoting specific immune responses.<sup>40</sup>

In another study, broccoli-derived nanoparticles (BDN) of plant origin were used to target DCs to inhibit DCs overactivation and induce immune tolerance by activating the adenosine monophosphate-activated protein kinase (AMPK) signaling pathway. The material blocked the differentiation of Gr1+ monocytes to pro-inflammatory CD11b+ DCs and effectively attenuated the inflammatory response. Both cellular and animal experiments in this study confirmed that BDN maintains immune homeostasis by specifically activating the AMPK pathway in DCs.<sup>41</sup> Structural parameters of nanomaterials require prioritized optimization in subsequent investigations to improve targeting precision and biocompatibility, while their clinical translation feasibility necessitates systematic evaluation.

## T Cells

The total number of T lymphocytes in the lung parenchyma and peripheral and central airways of patients with COPD is significantly increased, with a predominance of CD8+ cytotoxic T cells and CD4+ helper T cells, with a greater increase in CD8+ cells. During an immune imbalance, the infiltration of CD4+ and CD8+ cells into the airways is exacerbated, releasing large amounts of cytokines, exacerbating airway inflammation and promoting Airway remodelling, leading to a decrease in FEV1 and a correlation between the number of T cells and the severity of alveolar destruction and airflow obstruction.<sup>67,68</sup>

For example, it has been demonstrated that the use of *Asteromyces callus*-derived nanovesicles as natural nanocarriers, loaded with immunomodulatory nucleic acids, proteins or small molecules, can target T cells and their microenvironment, inhibit the proliferation and activation of CD4+ and CD8+ cells, and reduce the release of pro-inflammatory cytokines from them, which could reduce inflammatory responses and improve symptoms of the rat asthma model. In addition, the nanovesicles could further inhibit the over-activation of T cells by affecting the function of dendritic cells. Meanwhile, the vesicles indirectly altered the cytokine microenvironment by reducing the production of Th2-type cytokines (eg, IL-4, IL-5, IL-13) and pro-inflammatory cytokines (eg, TNF- $\alpha$ ) and promoting the secretion of the anti-inflammatory factor IL-10, which attenuated airway inflammation and airway hyperresponsiveness and improved asthma symptoms.<sup>42</sup> Based on the results of the asthma model, we speculate that nanovesicles may attenuate the inflammatory response by modulating T-cell behaviour in COPD. These studies not only validate the efficacy of nanomaterials in immunomodulation but also provide a theoretical basis for the development of novel nanomedicines targeting COPD.

## B Lymphocytes

While T cells dominate adaptive immunity in COPD, B lymphocytes contribute to chronic inflammation through autoantibody production. B lymphocytes play a key role in the inflammatory process of COPD through their production of antibodies and their involvement in lymphoid follicle formation.<sup>69</sup> Targeting B cells can effectively reduce the production of inflammatory mediators and thereby alleviate the symptoms of COPD. Specific targeting of B cells has been investigated using surface-modified anti-CD20 nanoparticles that bind to the CD20 antigen on B cells. This targeting strategy can deliver drugs directly to B cells, thereby reducing the inflammatory mediators secreted by B cells, such as tumour necrosis factor (TNF) and interleukin (IL), and thus alleviating the associated inflammatory response.<sup>43</sup> The pivotal regulatory role of B cells in immune response processes has been definitively elucidated, with their pathological mechanism involvement demonstrated to exert determinant influences during disease progression in autoimmune disorders and malignant neoplasms. As a novel drug delivery platform, the clinical advantages of nanocarriers have been systematically clarified, encompassing characteristics such as reduced drug toxicity, prolonged in vivo circulation half-life, and enhanced therapeutic efficacy.<sup>70</sup> Based on these technical attributes, the development of targeted nanomaterials for B-cell subsets in COPD has been prioritized in research agendas, where feasibility validation of this technical pathway provides a theoretical foundation for the establishment of novel therapeutic strategies in COPD management.

## Targeting Inflammatory Mediators

As a typical inflammatory disease, the pathologic complexity of COPD is not only reflected in the involvement of diverse inflammatory and structural cells as described previously, but also in the formation of a complex regulatory network by these cells through the release of inflammatory mediators. These mediators play a key role in the development of COPD through synergistic or antagonistic effects.<sup>30,71</sup> In COPD, the aberrant expression and action of inflammatory mediators (eg TNF- $\alpha$ , IL-6, IL-8, CRP, IL-1 $\beta$  and MCP-1, etc) form a complex network that together act on the relevant inflammatory cells, from initiating the inflammatory response to maintaining and amplifying the inflammatory response, to drive the chronic inflammatory process in COPD, leading to the gradual decline in lung function and disease progression in patients.<sup>72-77</sup> Nanomaterials engineered for the delivery of anti-inflammatory agents have demonstrated significant potential in modulating key inflammatory mediators. For example, one study successfully developed the ability to downregulate interleukin-1 receptor (IL-1R) and toll-like receptor (TLR) signalling pathways, such as IL-1 receptor-associated kinase (IRAK1) and TNF receptor-associated factor (TRAF6), after using nanocomposite micro-particles (NCMPs) nanoparticles to deliver miRNA-146a to the lung, thereby reducing the production of inflammatory cytokines (eg, IL-1 $\beta$ , IL-6 and IL-8), thereby inhibiting the inflammatory response<sup>78</sup> and providing new ideas for COPD treatment.<sup>79</sup> In investigating the potential of chitosan-encapsulated lipid carriers loaded with quercetin as an oral nanoplatform for depression management, quercetin-chitosan nanolipid carriers (QU-CS-NLCs) resulted in a significant reduction in the level of CRP, a marker of inflammation, by 65.4% in an LPS-induced depression model through enhanced anti-inflammatory delivery efficacy.<sup>80</sup> In another study, chitosan-coated solid lipid nanocapsules (SLN-chitosan) loaded with beriberi (Ber) were able to reduce inflammatory cell infiltration in bronchoalveolar lavage fluid (BALF), down-regulate pro-inflammatory cytokines, such as IL-1 $\beta$ , IL-6, IL-17, TNF- $\alpha$ , etc., and reduce myeloid oxidant levels. IL-1 $\beta$ , IL-6, IL-17, TNF- $\alpha$ , and other pro-inflammatory cytokines in BALF, as well as decreasing myeloperoxidase (MPO) activity and increasing superoxide dismutase (SOD) activity, which could reduce airway inflammation and oxidative stress, and create a new paradigm in the treatment of COPD.<sup>81</sup> Meanwhile, in an in vitro model of COPD induced by cigarette smoke extract (CSE), poly(lactic acid)-hydroxyacetic acid (PLGA) nanoparticles loaded with 18- $\beta$ -glycyrrhetic acid (18 $\beta$ GA) were able to reduce the generation of reactive oxygen species (ROS), down-regulate senescence-associated  $\beta$ -galactosidase (SA- $\beta$ -Gal) and p21, and reduce pro-inflammatory genes (CXCL1) and p21, while reducing the expression of CXCL1, IL-6, TNF- $\alpha$  and inflammation-related proteins (IL-8), and restored the expression of immunoregulatory factors such as IL-15, RANTES, and MIF, thus reducing oxidative stress, cellular senescence, and Airway inflammation, and exploring a new direction for the treatment of COPD.<sup>82</sup> Inflammatory mediators are pivotal to the pathological process of COPD, and nanomaterials have the potential to attenuate the inflammatory response by modulating the TLR signalling pathway and the expression of inflammatory mediators. This study not only validates the efficacy of nanomaterials in the treatment of COPD but also provides a theoretical basis for the development of novel nanomedicines. Future studies should optimize nanomaterial design to enhance specificity against key inflammatory mediators, improve targeted delivery to activated immune cells within COPD microenvironments, and evaluate clinical potential for suppressing inflammation-driven exacerbations.

## Oxidative Stress-Related

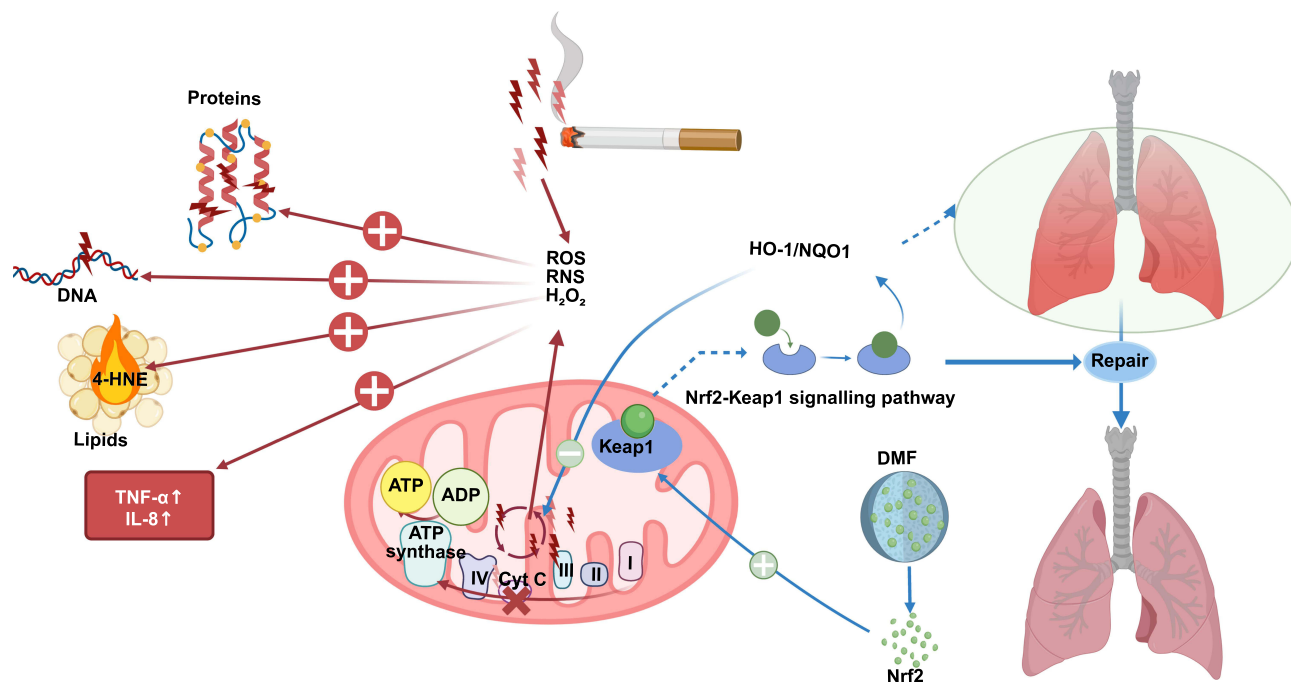
Beyond inflammation, oxidative stress exacerbates COPD via ROS-mediated damage to proteins, lipids, and DNA. Mitochondrial dysfunction further amplifies ROS production, thereby creating a self-perpetuating cycle.<sup>83</sup> Targets Oxidative stress plays a central role in the pathogenesis of COPD, and its main sources include the overproduction of reactive oxygen species (ROS) and reactive nitrogen species (RNS).<sup>84</sup> These substances can promote the expression of pro-inflammatory genes by directly damaging cellular components, such as proteins, lipids, and DNA, and by activating several signalling pathways, including transcription factors like NF- $\kappa$ B and histone acetyltransferases, thereby enhancing the inflammatory response in the lung. For example, ROS can increase the production of inflammatory factors by activating NF- $\kappa$ B and turning on the transcription of several inflammatory genes,<sup>85</sup> as well as promoting lipid peroxidation and generating reactive intermediates (eg, 4-hydroxy-2-enolenic aldehyde, 4-HNE) that further exacerbate lung tissue damage.<sup>84,86</sup> Cigarette smoke, a significant source of exogenous ROS, contains a large number of oxidants and free

radicals that directly contribute to oxidative stress.<sup>87</sup> In addition, mitochondria, as the primary site of energy supply in the cell, generate a certain amount of ROS during metabolism, and when mitochondrial function is impaired (especially when the electron transport chain is dysfunctional), this leads to overproduction of ROS, which is a major source of endogenous ROS. These excess ROS (superoxide anion  $O_2^-$  and hydrogen peroxide  $H_2O_2$ ) can accumulate intracellularly and cause oxidative stress, leading to damage to cellular proteins, lipids, and DNA, as well as activating a number of signalling pathways (eg, proteases such as caspase-3) and triggering apoptosis.<sup>88</sup>

Nanomaterials show promise in mitigating oxidative stress. By targeting and delivering antioxidants, nanomaterials can effectively mitigate oxidative damage in mitochondria.<sup>10</sup> Oxidative stress in mitochondria is closely related to the Nrf2 signalling pathway, which is involved in resisting oxidative stress-mediated injury and also regulates processes such as inflammation, calcium homeostasis, apoptosis, iron death, and mitochondrial oxidative stress. For example, as an Nrf2 activator, dimethyl fumarate (DMF) promotes the transcription of antioxidant genes by activating the Nrf2-Keap1 signalling pathway, which in turn reduces ROS production and inhibits mitochondrial oxidative stress-induced injury. In our studies, DMF nanoparticles were delivered to the lungs for their antioxidant effects using an aerosol dispersion technique<sup>89,90</sup> (Figure 1). This strategy provides a novel idea for the treatment of oxidative stress in COPD and demonstrates the unique advantages of nanomaterials in modulating complex oxidative stress networks. Oxidative stress plays a central role in the pathogenesis of COPD, and nanomaterials have the potential to attenuate oxidative stress damage through targeted delivery of antioxidants. These studies not only validate the efficacy of nanomaterials in regulating oxidative stress but also provide a theoretical basis for the development of novel nanomedicines for COPD.

## Proteases - Targets Related to an Imbalance in the Anti-Protease System

In the context of COPD, the release of neutrophil elastase (NE), proteinase 3, and histone B by neutrophils, along with matrix metalloproteinases (MMPs, eg, MMP-9, MMP-12) and histones (eg, cathepsin L and S) produced by macrophages, has been identified as a key factor in the destruction of lung tissue.<sup>91</sup> The excessive release of these proteases, in



**Figure 1** Mechanisms of DMF Activation of the Nrf2 Pathway Attenuate ROS Storm and Alleviate Lung Injury. DMF-loaded nanoparticles are delivered to the lungs via aerosol inhalation, enabling targeted release of DMF in pulmonary tissues. DMF binds to Keap1, disrupting the Keap1–nuclear factor erythroid 2-related factor 2 (Nrf2) complex and facilitating Nrf2 nuclear translocation. Nuclear Nrf2 activates the transcription of downstream antioxidant genes, including HO-1 and NQO1, thereby reducing ROS levels and RNS levels and mitigating mitochondrial oxidative damage. Created in BioRender. Qianyue, Z. (2025) <https://BioRender.com/rwyw3io>.

**Abbreviations:** DMF, dimethyl fumarate; Nrf2, nuclear factor erythroid 2-related factor 2; Keap1, Kelch-like ECH-associated protein 1; ROS, reactive oxygen species; RNS, reactive nitrogen species, HO-1, heme oxygenase-1; NQO1, NAD(P)H quinone dehydrogenase 1.

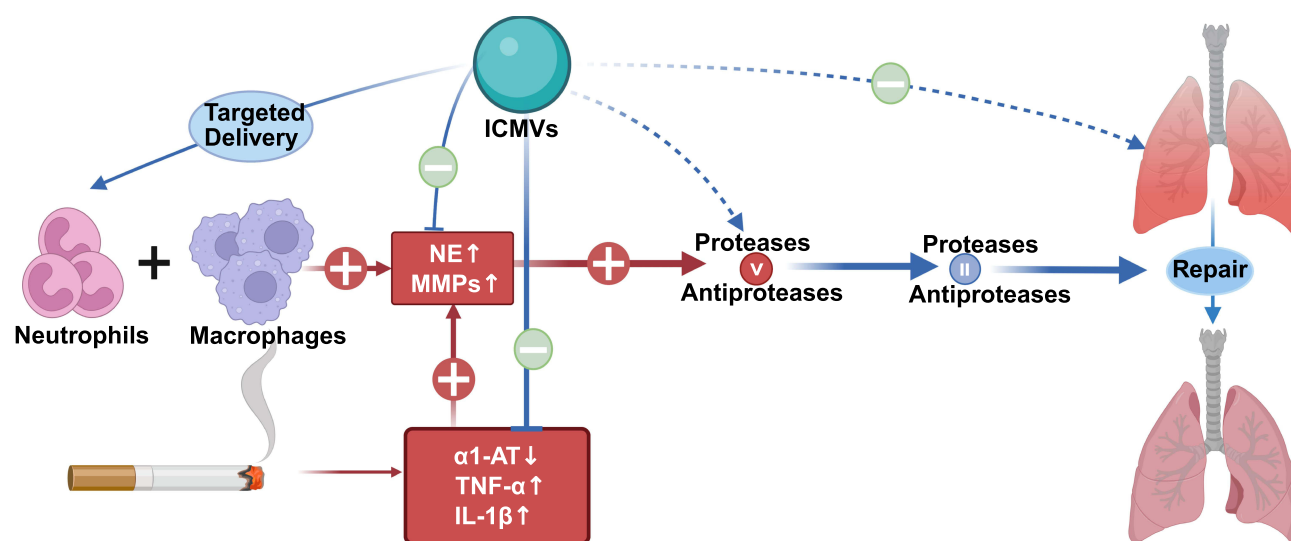
combination with the relative deficiency of antiproteases (eg,  $\alpha$ 1-antitrypsin,  $\alpha$ 1-AT), gives rise to a protease-antiprotease imbalance, which is a significant contributing factor to the progression of COPD.<sup>92</sup> Smoking, a major trigger of COPD, has been shown to both increase protease release and decrease the activity of  $\alpha$ 1-AT through oxidative effects. Concurrently, inflammatory cells release a substantial amount of inflammatory mediators (eg, TNF- $\alpha$ , IL-1 $\beta$ ) for production, and these mediators further promote the release of MMPs, which ultimately leads to the worsening of the imbalance.<sup>93–95</sup>

The targeting of the protease-antiprotease imbalance by nanomaterials has been demonstrated to show promising applications. For instance, lipid nanomaterials interbilayer-crosslinked multilamellar vesicles (ICMVs) loaded with sivelestat, an inhibitor of neutrophil elastase (NE), have been shown to deliver NE inhibitors through targeted delivery mechanisms, thereby prolonging the duration of drug action and significantly increasing its bioavailability. This nanomaterial has demonstrated the significant efficacy of sivelestat in a mouse model of LPS-induced endotoxic shock. Under conditions of significant NETs formation inhibition, the reduction in inflammatory mediator levels and improvement in murine survival rates were simultaneously observed (Figure 2). The inhibitory effect on NE activity has been verified to achieve cascade downregulation of secondary proteases (eg, matrix metalloproteinases) activities through modulation of inflammatory factor secretion networks, ultimately leading to the restoration of dynamic equilibrium in the protease-antiprotease system being accomplished.<sup>96</sup> Existing research data have not only allowed the theoretical foundation for COPD treatment paradigm innovation to be established, but also enabled the unique advantages of nanomaterials in inflammatory cascade regulation to be systematically revealed.

Nanotherapeutic strategies targeting proteases/inflammatory factors have been identified as potential intervention protocols for COPD. In subsequent studies, the targeting specificity and biosafety profiles of nanocarriers within COPD pathological microenvironments require prioritized elucidation, with the advancement of their clinical translation process thereby being realized.

## Targets Related to Airway Remodeling

COPD, as a chronic respiratory disorder with multidimensional pathological features, has had its core pathomechanisms clearly elucidated. The pivotal role of airway remodeling has been established through substantial research evidence.<sup>97,98</sup>



**Figure 2** Mechanisms of ICMVs Targeting of Protease-Antiprotease Imbalance Attenuates COPD Pathogenesis. ICMVs loaded with sivelestat, a NE inhibitor, deliver NE inhibitors via a targeted delivery mechanism to neutrophils and macrophages. Sivelestat binds to and inhibits NE, suppresses the activation of MMPs, and reduces the release of pro-inflammatory cytokines (TNF- $\alpha$ / [IL-1 $\beta$ ]). This cascade attenuates lung tissue damage and restores the protease-antiprotease homeostasis. Created in BioRender. Qianyue, Z. (2025) <https://BioRender.com/euz90h1>.

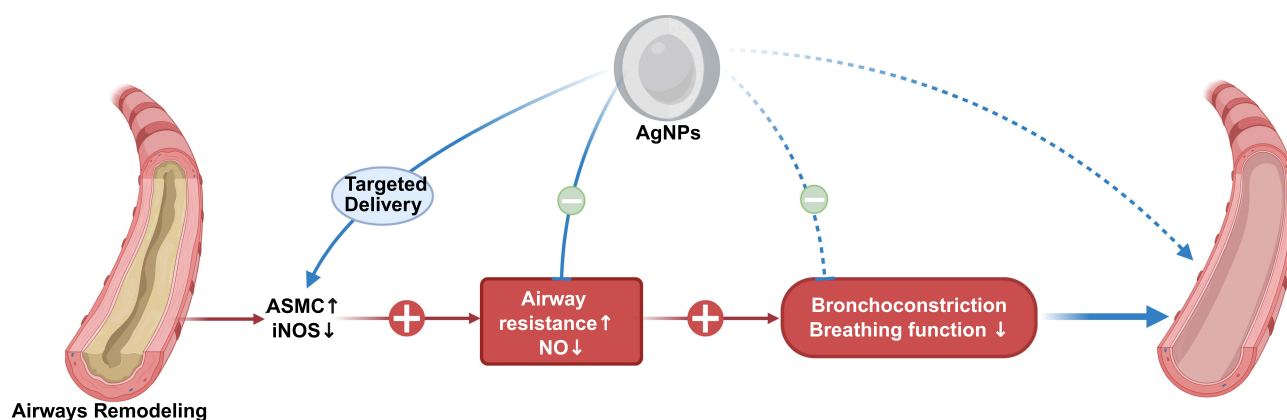
**Abbreviations:** ICMVs, Interbilayer-crosslinked multilamellar vesicles; NE, Neutrophil elastase; NETs, MMPs, Matrix metalloproteinases; TNF- $\alpha$ , Tumor necrosis factor-alpha; IL-1 $\beta$ , Interleukin-1 beta.

The interaction mechanisms among pathological elements, including epithelial cell injury, fibrotic progression, and structural alterations in smooth muscle, have been systematically elucidated. These elements have been demonstrated to collectively influence the spatiotemporal progression of airway remodeling through molecular network regulation, thereby exerting determinant effects on the clinical outcomes of COPD.<sup>3</sup> The chemotactic cascade reaction triggered by epithelial damage has been proven to significantly exacerbate the degree of airway obstruction.<sup>99</sup> Abnormal deposition of extracellular matrix (ECM) and compositional alterations at injury sites have been experimentally verified.<sup>100</sup> These modifications are achieved through mechanical property regulatory pathways, manifested as decreased airway elasticity and compliance, ultimately leading to enhanced airway wall stiffness. This pathological phenomenon has been confirmed to exhibit direct correlation with the formation of fixed stenosis and the deterioration of airflow limitation.<sup>101</sup> Aberrant proliferation and hypertrophy of airway smooth muscle have been identified as core driving factors in the remodeling process.<sup>102</sup> The thickening effect not only induces structural modifications of the airway wall but also results in markedly elevated ventilatory resistance, with consequent impairment of respiratory function being accomplished.<sup>103</sup> Epithelial cells, serving as critical regulatory units in airway remodeling, have their stem cell characteristics and plasticity activated through stromal interaction mechanisms, playing central roles in airway repair processes.<sup>104</sup> The susceptibility of COPD patient-derived epithelial cells to remodeling processes has been substantiated by multiple investigations, and the efficacy of nanomaterial-based pulmonary epithelial targeting strategies has been successfully validated. For example, nanoparticles such as multilamellar bodies, mesoporous nanoparticles, and liposomes can carry therapeutic agents (eg, drugs or DNA-expressing vectors), which can be delivered to the airway epithelial cells. This delivery system provides a viable clinical therapeutic approach for targeting damage to the respiratory epithelium in airway remodeling, promoting the repair and regeneration of epithelial cells and, by extension, targeted treatment of Airway remodelling.<sup>105</sup>

Furthermore, nanomaterials have shown potential in inhibiting fibrosis. For example, spermine-functionalized acetylated dextran nanoparticles (SpAcDex NPs) can target the NF $\kappa$ B signaling pathway in fibroblasts by delivering NF $\kappa$ B decoy ODN. This mechanism effectively inhibits the fibrotic process by blocking transforming growth factor-beta (TGF- $\beta$ )-mediated differentiation of fibroblasts into myfibroblasts while suppressing collagen synthesis and deposition.<sup>106</sup> The fibrotic therapeutic strategy in the airway remodeling process of COPD has been confirmed to provide a theoretical foundation for the application of nanomaterials. Through research verification, the development of multi-target synergistic therapeutic regimens based on the complex COPD microenvironment has been established as a key future research direction to achieve profound inhibition of Airway remodeling-associated fibrosis. During the pathological process of airway remodeling, the proliferation and hypertrophy of smooth muscle have been clearly identified as critical pathological features, rendering them potential targets for therapeutic intervention.

Through experimental studies, the biological behaviors of airway smooth muscle cells (ASMCs) have been found to be regulated by silver nanoparticles (AgNPs), specifically manifested as significantly upregulated expression of inducible nitric oxide synthase (iNOS), thereby achieving inhibition of ASMC proliferation and induction of apoptosis. This mechanism further confirms that the biosynthesis of nitric oxide (NO) is effectively promoted, subsequently generating significant effects in reducing airway wall thickness, decreasing airway resistance, and improving ventilation function (Figure 3). Notably, as a molecule with well-characterized bronchodilatory properties, the physiological functions of NO have been demonstrated to include alleviation of smooth muscle contraction and improvement of airway hyperresponsiveness.<sup>107</sup>

These findings enable the construction of novel therapeutic strategies for COPD-related airway smooth muscle hyperplasia. During COPD progression, the pathologically significant phenomenon of airway remodeling has been revealed to be amenable to multidimensional interventions through nanomaterials, encompassing precise targeting of epithelial cells, effective suppression of fibrotic processes, and dynamic regulation of smooth muscle proliferation. Through relevant studies, significant enhancement of drug utilization efficiency has been achieved, while innovative development of new therapeutic pathways for COPD has been accomplished. Subsequent research should prioritize the optimization of nanomaterial design, improvement of targeting specificity and safety profiles, and comprehensive exploration of clinical translation potential.<sup>108</sup>



**Figure 3** AgNPs Attenuate COPD Airway Remodeling via iNOS/NO-Mediated Inhibition of Smooth Muscle Hyperplasia. AgNPs target ASM cells, significantly upregulating inducible nitric oxide synthase (iNOS) expression, inhibiting ASM cell proliferation, and inducing apoptosis. The increased nitric oxide (NO) biosynthesis consequently reduces airway wall thickness, decreases airway resistance, thereby attenuating airway remodeling and improving ventilatory function. Created in BioRender. Qianyu, Z. (2025) <https://BioRender.com/em29uc2>.

**Abbreviations:** AgNPs, Silver nanoparticles; ASMCs, Airway smooth muscle cells; iNOS, Inducible nitric oxide synthase; NO, Nitric oxide.

## Application of Nanoparticles in COPD

The following five main categories of nanomaterials are currently employed in the treatment of COPD: polymer nanoparticles, dendrimers, inorganic nanoparticles, lipid nanoparticles (LNP), and bioactive nanoparticles of plant origin. The unique physicochemical properties and functionalized design of these materials enable them to target and regulate the core pathological mechanisms of COPD, such as the inflammatory cascade, oxidative stress, and protease imbalance. This has the potential to significantly enhance therapeutic precision and efficacy.<sup>109,110</sup> The subsequent section will systematically analyse their mechanism of action and research progress.

### Polymer Nanoparticles

Among polymer nanoparticles, polylactic acid-hydroxyacetic acid copolymer (PLGA) nanoparticles have been the focus of research and application due to their biodegradable structure consisting of lactic acid and hydroxyacetic acid linked by ester bonds.<sup>111</sup> Through precise structural design and functional optimisation, PLGA nanoparticles can achieve targeted drug delivery. Experimental results demonstrated that PLGA-targeted PINP nanoparticles exhibited significantly higher neutrophil-targeted delivery efficiency compared to non-targeted PNPs, with a 6.5-fold increase (17.58% vs 2.72%,  $p < 0.001$ ), as well as controlled release and improved stability. This significantly enhances their unique advantages in the treatment of COPD.<sup>34</sup>

The nanoscale properties of PLGA nanoparticles have been demonstrated to enhance drug efficacy and reduce side effects, thereby significantly improving patients' therapeutic experience.<sup>112-114</sup> Specifically, in a study by Mohamed et al, the inflammatory process in COPD was targeted through the loading of miR-146a into PLGA nanoparticles. The application of miR-146a nanoparticles was confirmed by experimental data to induce a significant reduction in interleukin-1 receptor-associated kinase 1 (IRAK-1) gene expression levels, with precise regulation of inflammatory responses being achieved through this mechanism.<sup>79</sup> The construction of poly(lactic-co-glycolic acid) (PLGA) nanoparticles was accomplished in related studies, and the encapsulation of the anti-inflammatory drug bunofen was realized via this nanocarrier, while the therapeutic targeting of neutrophil-mediated inflammatory responses in COPD was established through this strategy.<sup>115</sup> Lipopolysaccharide (LPS)- and cigarette smoke-induced lung injury was demonstrated to be markedly alleviated by this nanodrug delivery system, with its therapeutic potential for COPD being further validated through animal experimental data.<sup>34</sup> The clinical translational value of the PLGA-based nanotherapeutic system was substantiated by existing research findings, and the implementation of additional clinical trials was recommended to systematically evaluate the efficacy parameters and safety profile of this nanosystem in COPD treatment.<sup>116</sup>

## Dendrimers

Dendritic macromolecules, as a class of synthetic branched topological polymers, exhibit a three-dimensional architecture systematically constructed with a central core layer, internal repeating unit layers, and peripheral functional unit layers. Alcohol chain-modified polyamidoamine (PAMAM) and polyphenylene ether (PPE) are classified as canonical therapeutic modification forms within this category.<sup>117</sup> The endowment of multifunctional properties is achieved in these macromolecules through surface functionalization design strategies, leading to a significant expansion of their application potential in drug delivery systems and biomedical domains.<sup>118</sup>

Au-PAMAM dendrimer nanocomposites demonstrate antioxidant properties conclusively superior to gold-core polypropylene imine (PPI) dendrimers and ascorbic acid controls. Quantitatively, the oxidative degradation rate constant of Au-PAMAM dendrimers was determined to be 85-fold higher than that of ascorbic acid, a magnitude difference that fully elucidates their unique advantage as drug delivery systems for selective targeting of oxidative stress. The efficacy of this nanosystem in precision regulation of oxidative stress responses has been experimentally validated, with pathophysiological mechanisms underlying its therapeutic application in chronic obstructive pulmonary disease (COPD) being established.<sup>119</sup> Consequently, the feasibility of pioneering novel COPD treatment paradigms has been rigorously proposed based on these findings.<sup>117,120</sup>

## Inorganic Nanoparticles

Significant advantages in disease diagnosis and therapeutic delivery applications have been demonstrated by inorganic nanoparticles comprising precious metal species (eg, aurum, argentum), ferric oxide derivatives, and silica-based architectures, which are fundamentally attributed to their distinctive physicochemical property profiles.<sup>121,122</sup> Mesoporous silica nanoparticles (MSNs) are important carriers for targeted delivery in the lungs due to their high specific surface area (~1000 m<sup>2</sup>/g), tunable pore size (2–30 nm), and easy functionalization of surface silanol groups. Studies have shown that MSNs can escape alveolar macrophage phagocytosis via polyethylene glycol (PEG) modification and enhance mucus layer penetration via mucin-penetrating peptides, significantly increasing lung drug residence time (from <2 h to >6 h) and bioavailability (from <15% to >50%).<sup>123,124</sup> In related studies, researchers have also used rare earth metals such as cerium oxide (CeO<sub>2</sub>), whose unique cubic fluorite crystal structure and Ce<sup>3+</sup>/Ce<sup>4+</sup> redox cycling properties give it excellent antioxidant and catalytic properties. Cerium nanoparticles (CeNPs) mimic the activities of endogenous antioxidant enzymes (eg, SOD and catalase), reduce oxidative damage by scavenging reactive oxygen species (ROS), and activate the Nrf2/ARE pathway to enhance cellular antioxidant defence mechanisms.<sup>125</sup>

In addition, iron oxide nanoparticles (IONPs) have potential in COPD airway inflammation modulation due to their superparamagnetic properties, which allow precise aggregation at the focal site via an external magnetic field, as well as the modification of anti-inflammatory peptides (eg, chlorotoxins) on their surface to improve targeting.<sup>126</sup> The suppression of nuclear factor κB (NF-κB) activation and NLRP3 inflammasome pathways has been demonstrated to mediate the downregulation of pro-inflammatory cytokine expression (eg, TNF-α, IL-1β) through cerium oxide nanoparticle (CeNP) intervention.<sup>127</sup> Ideal therapeutic candidacy for chronic obstructive pulmonary disease (COPD) management is conferred upon these nanostructures by their synergistic antioxidant/anti-inflammatory capacities coupled with precisely programmable surface functionalization modalities.

## Lipid Nanoparticles (LNPs)

Significant therapeutic advantages in chronic obstructive pulmonary disease (COPD) management have been demonstrated through strategic optimization of auxiliary lipid constituents (DOPC/DOPS) in lipid nanoparticle (LNP) formulations.<sup>128</sup> Targeted delivery to bronchial epithelial cells is specifically enabled by the engineered RNA encapsulation efficiency of these nanostructured systems, with concomitant minimization of off-target systemic effects. These nanoparticles are capable of delivering anti-inflammatory mRNAs (eg, IL-10) or silencing inflammation-related siRNAs (eg, NF-κB).<sup>129,130</sup> For example, Tam et al showed that DOPS-LNP delivery of siRNA resulted in a more than 90% reduction in the expression of target proteins and significantly suppressed the chronic inflammatory response. After nasal delivery, luciferase expression in the nose and lung increased tenfold, suggesting that LNPs are suitable for localised therapy in COPD.<sup>131</sup>

In addition, Ongun et al further optimised the PEG lipid content (1.5 mol%) to avoid inhibition of cellular uptake while maintaining the stability of LNP nebulisation, providing a novel strategy for precise delivery to deep airways such as terminal fine bronchi and alveoli.<sup>132</sup> Future studies should focus on further validating the long-term efficacy and safety of LNPs in animal models of COPD and exploring the synergistic effects of adjuvant lipids with PEG to accelerate the clinical translation of gene therapy with LNPs.<sup>133,134</sup>

## Plant-Based Nanoparticles

Clinical management of COPD is challenged by the limited efficacy and significant side effects of traditional medications, prompting plant-derived biocomponents to become the focus of emerging therapeutic strategies. Nanoformulations based on plant active ingredients provide a new paradigm for efficient and low-toxicity therapy by enhancing bioavailability, enabling precise lung targeting, providing controlled release protection and synergistic effects, significantly improving COPD lung function indices (eg, FEV<sub>1</sub>), inhibiting inflammatory factors (eg, IL-6/TNF- $\alpha$ ), and reducing acute exacerbation frequency. The effectiveness of this strategy in plant-derived drug delivery has been well-studied.<sup>135–138</sup> Taking liquorice (*Glycyrrhiza glabra*) as an example, the main active component of this common medicinal plant, 18- $\beta$ -glycyrrhizic acid (18 $\beta$ GA), exhibits multiple pharmacological effects such as anti-inflammatory, antioxidant, and antiviral effects,<sup>139</sup> providing a scientific basis for its use in the treatment of COPD. It was shown that 18 $\beta$ GA-loaded poly(lactic acid)-hydroxyacetic acid copolymer (PLGA) nanoparticles significantly suppressed the inflammatory response by inhibiting NF- $\kappa$ B nuclear translocation and reducing cytokine expression in an *in vitro* model of cigarette smoke-induced COPD. In addition, this study found that 18 $\beta$ GA-PLGA nanoparticles significantly reduced CSE-induced reactive oxygen species (ROS) generation. Specifically, 5% cigarette smoke extract significantly increased intracellular ROS levels in BCiNS1.1 cells, while ROS generation was reduced by 39.5% after pretreatment with 18 $\beta$ GA-PLGA nanoparticles, further emphasising the significant benefits of plant-based nanoparticles in antioxidant therapy.<sup>82</sup>

The cigarette smoke extract (CSE)-induced elevation of reactive oxygen species (ROS) levels in 16HBE bronchial epithelial cells and RAW264.7 macrophages was demonstrated to be effectively suppressed by berberine (BBR)-incorporated liquid crystalline nanoparticles (BBR-LCNs).<sup>140</sup> A dose-dependent reduction in ROS generation was observed through pretreatment experiments, with concomitant significant neutralization of CSE-triggered oxidative stress. In CSE-stimulated 16HBE cells, upregulated gene expression of inflammatory cytokines, including IL-1 $\beta$ , IL-6, and TNF- $\alpha$ , was identified, whereas transcriptional levels of these mediators were markedly suppressed following BBR-LCNs pretreatment. Concurrent detection of decreased TNF- $\alpha$  gene expression and reduced nitric oxide (NO) production in RAW264.7 cell models further corroborated the anti-inflammatory efficacy, establishing the therapeutic potential of botanically derived nanomaterials in COPD management through dual antioxidative/anti-inflammatory mechanisms.<sup>141</sup> The molecular pathways underlying these formulations' actions in COPD pathogenesis require elucidation, while their safety profiles and therapeutic outcomes necessitate systematic validation via clinical trials to facilitate expansion of clinical translation pathways for plant-based nanotherapeutics.<sup>142</sup>

## Conclusion and Outlook

In the field of COPD, nanomedicines have gradually moved from proof-of-concept to clinical translation, in which inhalable nanoparticle formulations have been realized for precise delivery through devices such as dry powder inhalers, which are advancing clinical trials in COPD by virtue of the advantages of controllable particle size and strong targeting.<sup>143–147</sup> A recent Phase II study showed that dexamethasone liposome nanoparticles (Lipo-Dexa) specifically targeted alveolar macrophages, reducing inflammatory factor levels by 60%.<sup>148</sup> The nebulized inhalation route, on the other hand, creates high local concentrations in the lungs and significantly reduces systemic toxicity.<sup>149,150</sup> However, clinical translation still faces multiple challenges and bottleneck, not only the optimization of drug encapsulation rate and stability, lung physiological barrier breakthrough, the guarantee of inter-batch consistency of physicochemical properties in large-scale production, biosafety also warrants attention, as studies have demonstrated that seven-day exposure of murine lungs to aluminum oxide nanoparticles (Al<sub>2</sub>O<sub>3</sub> NPs) results in emphysema and small airway remodeling, accompanied by exacerbated inflammation and apoptosis,<sup>151</sup> and the harmonization of regulatory standards, which

constrains its clinical translation, highlighting the potential of nanomedicines for clinical development in this field and the problems to be solved, as well as technical and cost challenges of adapting to the heterogeneity of patients in personalized medicine, all of which need to be solved through cross-subsidization and cross-subsidization.<sup>20–22,25,152</sup> At the same time, the technical and cost challenges of adapting to patient heterogeneity in personalized medicine need to be gradually solved through interdisciplinary collaboration and technological innovation.<sup>12</sup>

Nanocarriers operate in COPD therapy via three core mechanisms: targeted delivery (enhancing lesion-specific recognition through surface chemistry modifications, improving drug-loading efficiency<sup>153</sup>), slow-release modulation (sustaining therapeutic effects via controlled biodegradation, validated by in vitro success<sup>154</sup>), slow-release modulation (sustaining therapeutic effects via controlled biodegradation, validated by in vitro success<sup>155</sup>).<sup>156,157</sup> Despite these advances, clinical translation faces critical barriers: (1) low target retention rates limiting drug efficacy,<sup>158</sup> (2) nanomaterial toxicity risks, exemplified by silica nanoparticles (SiNPs) inducing lung fibrosis (150% collagen increase, 1.8-fold TGF- $\beta$  upregulation, \* $p$ \* $<$ 0.05) and systemic Th2 inflammation (2-fold mast cell accumulation, \* $p$ \* $<$ 0.05) in murine models,<sup>159–162</sup> and (3) stringent FDA regulations delaying development.<sup>163</sup>

Future efforts must prioritize intelligent stimulus-responsive systems for inflammation-triggered drug release,<sup>164,165</sup> expand applications to asthma, lung cancer, and infections,<sup>166</sup> and integrate AI-driven genomic/proteomic analysis with computational nanomedicine optimization to enable etiology-specific precision therapies, as demonstrated in oncology.<sup>167</sup> These interdisciplinary strategies promise to accelerate translational pipelines, advancing COPD-specific nanotherapeutics toward clinical reality.<sup>168</sup> Focusing also on the key role of interactions between axes of pathology in driving COPD progression, could such interactions be a key consideration in the design of holistic nanotherapies? The hypothesis becomes reality that therapies can target multiple pathways simultaneously, breaking the self-perpetuating cycle of the disease.<sup>169,170</sup> Such interdisciplinary innovations are poised to accelerate the translational trajectory of nanomedicine from bench to bedside, ultimately enabling precision therapeutics for respiratory disorders.

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## Disclosure

The authors report no conflicts of interest in this work.

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