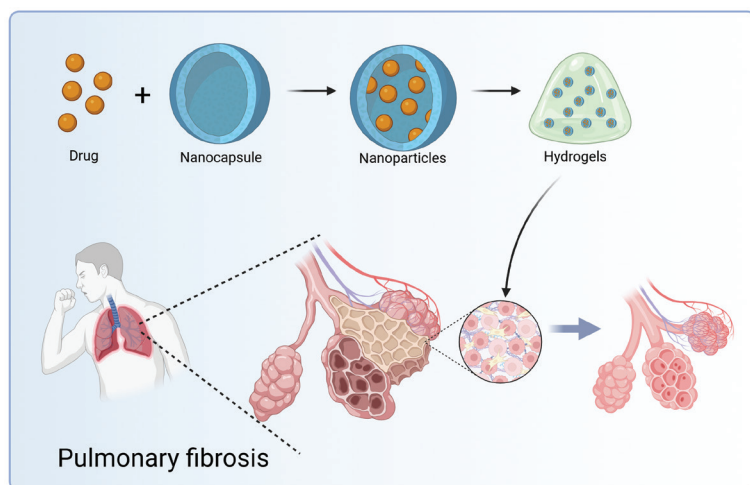


Targeted Drug Delivery System for Pulmonary Fibrosis: Design and Development of Biomaterials

Graphical abstract



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In brief

Pulmonary fibrosis therapies are revolutionized by biomaterial-based targeted drug delivery systems. Nanocarriers, hydrogels, and biological carriers enhance drug specificity, reduce toxicity, and prolong efficacy. Key challenges include immune evasion and ECM penetration. Interdisciplinary approaches integrating nanotechnology, disease models, and precision medicine promise to overcome current limitations, paving the way for personalized, transformative PF treatments.

Highlights

- Current PF therapies (pirfenidone/nintedanib) face systemic toxicity and limited efficacy.
- Nanocarriers (liposomes, polymeric NPs) enhance drug penetration and retention in fibrotic lungs.
- Hydrogels enable sustained anti-fibrotic drug release at inflammation sites.
- Bio-carriers (exosomes, stem cells) improve biocompatibility and anti-inflammatory effects.
- Challenges: Immune clearance, stability, and ECM barriers hinder clinical translation.
- Precision medicine and stimulus-responsive biomaterials offer future therapeutic breakthroughs.

Targeted Drug Delivery System for Pulmonary Fibrosis: Design and Development of Biomaterials

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Abstract

Pulmonary fibrosis (PF) is a progressive interstitial lung disease characterized by excessive extracellular matrix deposition and tissue scarring, and leading to impaired lung function and respiratory failure. Although current treatments, such as pirfenidone and nintedanib, slow disease progression, they fail to completely halt or reverse fibrosis. Therefore, innovative therapeutic strategies are needed. Targeted drug delivery systems (TDDSs) are emerging as promising solutions. Biomaterials play critical roles in these systems by enhancing drug specificity, availability, and efficacy, while minimizing systemic toxicity. The most notable biomaterials include nanotechnology-based systems, including liposomes and polymeric nanoparticles, which facilitate drug penetration and slow release in fibrotic tissues. Hydrogels have three-dimensional structures providing controlled and sustained drug release at inflammation sites, and therefore are particularly valuable in PF treatment. Furthermore, biological carriers such as stem cells and extracellular vesicles have biocompatibility and anti-inflammatory effects that improve therapeutic outcomes. Despite the promising potential of these systems, clinical translation is hindered by several challenges, including immune clearance, stability of delivery platforms, and optimization of drug retention within diseased tissues. Interdisciplinary approaches integrating precision medicine with advancements in biomaterials may provide solutions opening new avenues for PF treatment. This review discusses current developments in targeted drug delivery for PF, emphasizing the importance of biomaterials, the mechanisms and barriers involved in pulmonary drug delivery, and future perspectives for overcoming current limitations. The ultimate goal is to improve patient outcomes by revolutionizing the approach to PF treatment through advanced drug delivery technologies.

Keywords

Biomaterials, nanoparticles, precision medicine, pulmonary fibrosis, targeted drug delivery.

Introduction

Overview of pulmonary fibrosis and its clinical challenges

Pulmonary fibrosis (PF) is characterized by scar tissue formation in the lung parenchyma, thus resulting in respiratory difficulties [1]. PF frequency increases as the population ages [2]. Fibrosis is particularly detrimental because of its correlation with elevated lung cancer risk [3]. In a large Korean population study, lung cancer was found in 1.2% of the general population, but 5% of patients with emphysema and almost 6% of patients with fibrosis [4]. Patients with both emphysema and fibrosis have a 12% increased risk of developing lung cancer compared to those with either condition alone [5]. One study [6] has demonstrated an approximately 5-fold

elevation in lung cancer incidence among individuals with an autoimmune condition; however, whether this elevation is due to immunosuppression or fibrosis is unclear. Because the cumulative cancer risk in these individuals escalates over time, and the longevity of patients with PF has increased with newly authorized anti-fibrotic therapies, the incidence of lung cancer in this population is anticipated to rise [7, 8].

The incidence of lung cancer among individuals with PF varies between 4.4% and 13%, and has been found to be as high as 48% in postmortem examinations [9, 10]. PF, referred to as interstitial lung abnormalities, was first associated with elevated cancer risk in the National Lung Screening Trial, which reported an adjusted incidence rate ratio of 1.33 [9, 11]. Individuals with idiopathic pulmonary fibrosis (IPF) have elevated risk of developing lung cancer with a poor prognosis and low survival rate [12, 13]. Patients with IPF who undergo single lung transplantation

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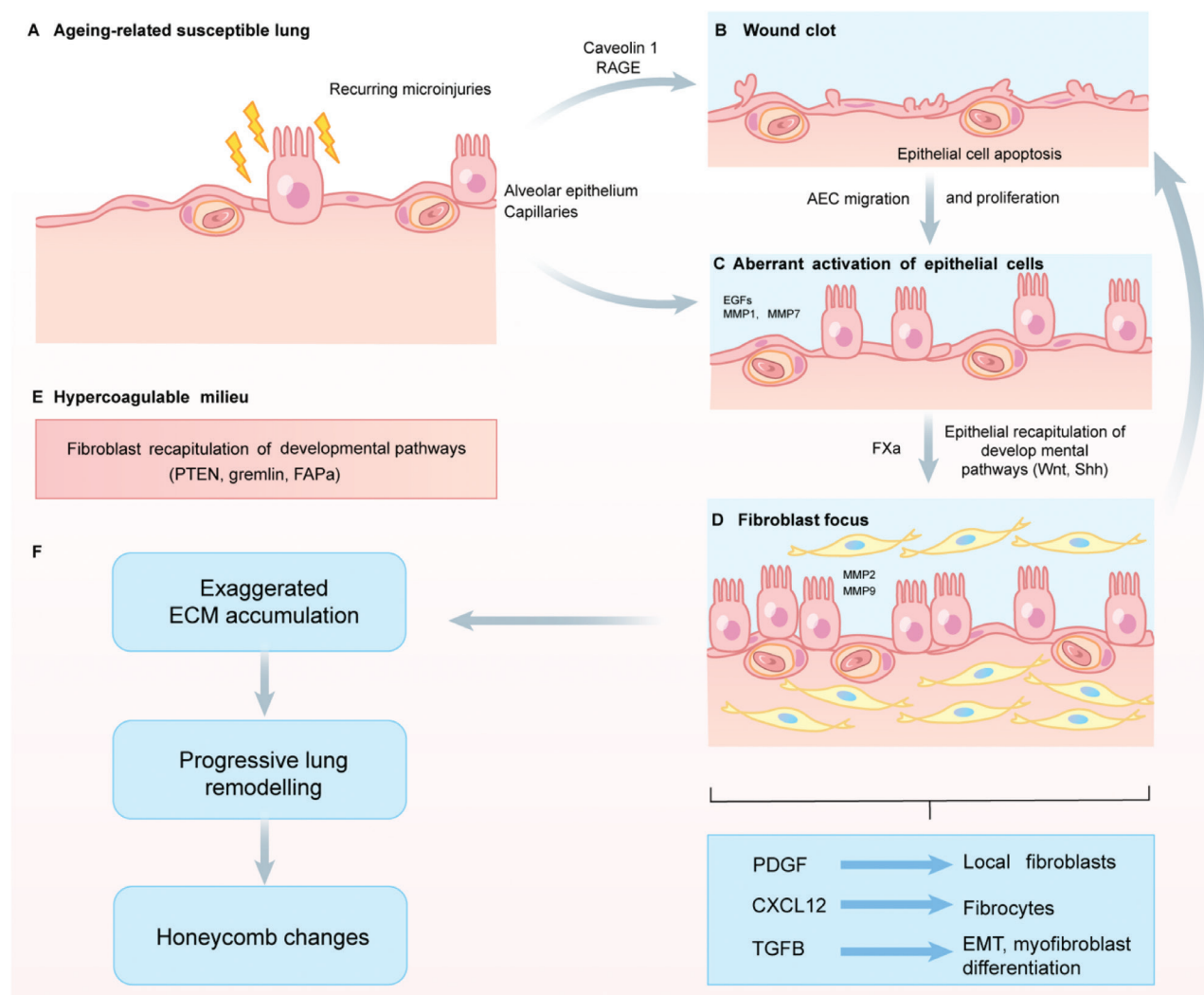


Figure 1 Proposed mechanisms in the pathogenesis of idiopathic pulmonary fibrosis.

are more than 20-fold more likely to develop lung cancer than the general population [14]. In a retrospective study [15], one-third of 900 patients diagnosed with lung cancer had PF.

Pathogenesis and therapeutic targets for PF

The pathogenesis of PF involves abnormal activation of the TGF- β signaling pathway, which promotes ECM excessive deposition by inducing epithelial mesenchymal transition (EMT) and fibroblast activation (Figure 1). In EMT, epithelial cells lose their polarity and acquire a mesenchymal phenotype, in a critical step in fibrosis development [16]. Excessive extracellular matrix (ECM) proteins, such as collagen, are produced by these myofibroblasts, thus leading to lung tissue thickening [17, 18]. The fibrotic process is mediated primarily by transforming growth factor beta (TGF- β), a cytokine that activates fibroblasts and promotes ECM deposition [19]. Other cytokines, such as IL-13, vascular endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF), play major roles in driving fibrosis [20]. Additionally, immune cells, such as neutrophils, macrophages, and T-cells,

are activated in response to lung injury, and contribute to chronic inflammation and fibrosis through the release of pro-fibrotic cytokines and growth factors [21].

Therapeutic strategies for PF focus primarily on modulating such pathways. Interventions targeting TGF- β signaling are a key therapeutic approach. Receptor inhibitors or antibodies to TGF- β have shown potential in preclinical and clinical studies [22, 23]. Other strategies include blocking the differentiation of fibroblasts into myofibroblasts, inhibiting collagen synthesis, and modulating matrix metalloproteinases, which degrade ECM components [23]. Additionally, therapies targeting specific cytokines, such as IL-13 inhibitors, have emerged as potential treatments that modulate the immune response and limit fibrosis progression [24]. These therapeutic approaches are aimed at decreasing the burden of fibrosis, and improving quality of life in patients with PF.

Current limitations of available treatments

Drugs that decrease immune system hyperactivity are the major method used for IPF management [25]. The rate of

Table 1 Summary of Conventional Drug Classes, and their Purposes, Mechanisms, and Limitations in the Management of PF [51–54]

Drug Class	Examples	Purpose	Mechanism of Action	Limitations
Corticosteroids	Prednisone	Decrease inflammation in lung tissue	Suppress immune response and inflammation	Limited efficacy in reversing established fibrosis; long-term adverse effects such as osteoporosis and diabetes
Immunosuppressants	Azathioprine, cyclophosphamide	Suppress immune-mediated damage	Decrease immune cell activity to limit tissue damage	Risk of infection, liver toxicity, and bone marrow suppression
Antioxidants	N-Acetylcysteine	Decrease oxidative stress	Act as a precursor to glutathione, protecting lung cells	Limited efficacy when used alone
Antifibrotic agents	Pirfenidone, nintedanib	Slow progression of fibrosis	Inhibit fibroblast activity and decrease collagen production	Considered newer agents; historically not part of conventional treatment
Supportive therapies	Oxygen therapy, antibiotics, diuretics	Manage symptoms and complications	Support breathing, manage infections, or decrease lung fluid	Do not treat fibrosis directly; primarily address symptoms

damage to lung tissue can be decreased by mitigating the intensity of this immune reaction, as previously described in a pathogenesis analysis [26]. This aspect is fundamental in addressing the root immunological defect. The prime aim of this strategy is to prevent or decrease the onset of scarring in the lungs [27]. Therefore, antifibrotic drugs, such as nintedanib and pirfenidone, are the treatments of choice for IPF, because no cure for the disease is yet available [28, 29]. The drugs decrease lung tissue inflammation and fibrosis, thus improving pulmonary function and quality of life among patients with PF [30].

The Food and Drug Administration [31] has approved pirfenidone as an orally active drug for IPF management [32]. Pirfenidone is usually taken as a capsule formulation at a dose of 267 mg, three times daily with food [33]. Current clinical trial evidence indicates that pirfenidone can address patient needs by slowing IPF progression and improving pulmonary function [34]. Nintedanib, another antifibrotic drug approved by the Food and Drug Administration for IPF [35], comes in capsule form and should be taken with meals at a dosage of 150 mg twice daily [36]. Pirfenidone and nintedanib decrease the lung function decline and therefore affect quality of life among patients with IPF [29]. Both agents are tyrosine kinase inhibitors originally developed during the discovery of cyclin-dependent kinase-4 inhibitors for lung cancer [37]. The inhibition of tyrosine kinase activity decreases the proliferation and differentiation of fibrotic cells [38, 39]. However, other treatments beyond antifibrotic agents may be necessary to control PF symptoms. These treatments comprise corticosteroids, or immunosuppressive and bronchodilator therapy, depending on individual patients’ needs [40, 41].

The effectiveness of these medications is limited, because they neither cure the illness nor revert pre-existing lung damage [42]. Although these drugs have been found to mitigate the decline in lung function, some individuals may exhibit no response, whereas others may react to differing extents [43]. Although these medications have been found to alleviate the diverse symptoms of IPF, they are associated with adverse effects [44]. Patients have reported substantial episodes of diarrhea after a 300-mg dose of nintedanib [45]. The

adverse effects may be severe and necessitate cessation of treatment [46, 47]. Interactions of nintedanib with anticoagulants, such as low-dose preventive heparin, have been found to increase the risk of bleeding, thrombosis, and thrombocytopenia [48]. Nintedanib inhibits VEGF, thereby decreasing platelet activity and leukocyte adhesion, and increasing the risk of hemorrhage and thrombosis [49]. In another study, 29.2% of patients had cutaneous rashes after pirfenidone administration [33, 50]. **Table 1** provides a concise overview of conventional therapies, and their roles, mechanisms, and limitations in PF management.

Traditional pharmacologic therapies for PF are aimed primarily at minimizing inflammation, inhibiting immune-mediated injury, and slowing the progression of fibrosis. As outlined in **Table 1**, these drug categories consist of corticosteroids, immunosuppressants, antioxidants, and antifibrotic drugs [55, 56]. Although these treatments contribute to symptom control and disease delay, they are frequently subject to considerable limitations. Corticosteroids and immunosuppressants, for example, may elicit serious long-term adverse effects such as osteoporosis, diabetes, and heightened vulnerability to infection [57, 58]. Antioxidants such as N-acetylcysteine have also shown limited benefit as monotherapies [59]. Whereas antifibrotic drugs, such as pirfenidone and nintedanib, have brought treatment advancements, their systemic delivery can result in gastrointestinal upset, liver injury, and poor patient compliance because of adverse effects [60]. Emerging drug delivery system (DDS) strategies involving nanoparticle formulations, liposomes as carriers, and inhalation-based delivery modes have shown promise in enhancing drug persistence in lung tissue, optimizing therapeutic efficacy, and minimizing adverse effects [61]. Through localized drug delivery and controlled release, such systems present a viable substitute for systemic administration [62, 63]. Ongoing research in these emerging technologies is important to maximize treatment outcomes and enhance patient quality of life.

Pirfenidone and nintedanib have low solubility and inconsistent pharmacokinetic profiles in conventional administration vehicles such as capsules and tablets [64]. Nintedanib

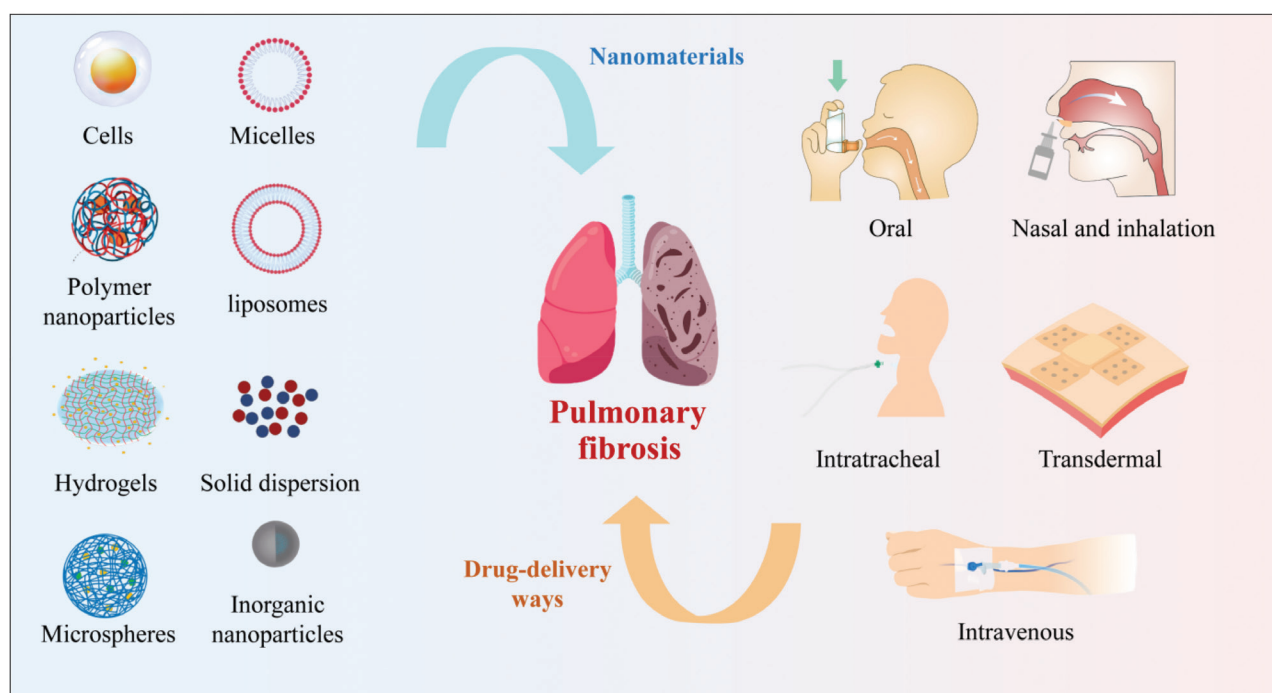


Figure 2 Advanced drug delivery systems for PM.

has low oral bioavailability (<5%) and significant first-pass metabolism resulting in the formation of the major metabolite BIBF1202, which is active but less effective than nintedanib [41, 65]. Nintedanib has shown an eight-fold increase in C_{max} and area under the curve in individuals with mild hepatic impairment; therefore, its use is not recommended for this population [37, 66]. Because of the limitations of these drugs, supplementary therapeutic alternatives that benefit patients with IPF are needed [40]. Clinicians should meticulously evaluate the risks and benefits of each medicine to optimize IPF treatment.

Advanced drug delivery systems

Nanoparticles: versatile carriers for targeted pulmonary therapy

Nanoparticles (such as PLGA and liposomes) and hydrogels, through their controlled release characteristics, can achieve targeted delivery of anti-fibrosis drugs (such as pirfenidone) to fibrotic lesions (Figure 2). Their diminutive size, elevated surface-area-to-volume ratio, and adjustable surface characteristics make them ideal candidates for pulmonary drug administration [55]. Biodegradable polymers such as polylactic-co-glycolic acid are widely used for controlled and sustained drug release [67–69]. These nanoparticles may contain anti-fibrotic agents such as pirfenidone or nintedanib, thus facilitating targeted drug delivery to fibrotic lung tissues. Targeted delivery decreases systemic exposure and related adverse effects, and is particularly advantageous for chronic illnesses such as PF. These

biodegradable carriers are highly effective in the administration of anti-inflammatory medications in COPD [70, 71]. Liposomes, lipid-based nanoparticles, are highly effective in encapsulating hydrophobic drugs, thus improving drug solubility and stability. For example, liposomal formulations of corticosteroids have shown enhanced retention in inflamed and fibrotic lung tissues, thus decreasing systemic toxicity [72, 73]. Gold and silver nanoparticles' unique optical and thermal properties make them suitable for targeted therapy [74]. For example, polyethylene glycol (PEG)-coated gold nanoparticles have been used to deliver chemotherapeutic agents such as cisplatin directly to lung tumors, thus decreasing systemic toxicity [75]. pH-sensitive nanoparticles have been developed to release drugs in the acidic microenvironment of fibrotic tissues, thereby ensuring targeted delivery and minimizing off-target effects [76].

Hydrogels: sustained release for chronic pulmonary diseases

Hydrogels are hydrophilic polymeric materials that can absorb significant quantities of water or biological fluids and can be used to construct three-dimensional networks. These features make hydrogels an excellent choice for regulated and sustained medication release, particularly in chronic pulmonary illnesses [77, 78]. Injectable hydrogels loaded with anti-fibrotic drugs have been explored for localized therapy in PF. These hydrogels provide sustained drug release over a period of weeks, thus decreasing the frequency of administration and improving patient compliance [79, 80]. For example, pirfenidone-loaded hydrogels have shown prolonged drug release and decreased fibrotic markers in preclinical models [81].

Because these hydrogels undergo a sol-gel transition at body temperature, they are ideal for pulmonary drug delivery.

They can be used to deliver antibiotics or anti-fibrotic agents directly to the lungs, thereby ensuring site-specific action and minimizing rapid clearance [82, 83]. Hydrogels can provide targeted delivery of antibiotics to treat bacterial lung infections, and can facilitate site specific action and slow rapid pharmaceutical clearance [84]. Oxygen-releasing hydrogels have been developed to alleviate hypoxic stress, a hallmark of fibrotic lung tissue, and to improve tissue oxygenation, which is critical for resolving fibrosis [85]. Oxygen gradually released from hydrogels alleviates hypoxic stress and enhances tissue oxygenation [86].

Biological carriers: harnessing natural mechanisms

To enhance drug delivery, both exosomes and nanoparticles enveloped with cell membranes, use existing natural systems. These systems are particularly suitable for precision medicine applications because of their high efficiency, biocompatibility, ability to avoid immune detection, and targeting abilities [87]. Spontaneously released vesicles called exosomes can be used to transport therapeutic compounds to fibrotic lung tissues [88, 89]. For example, exosomes carrying anti-inflammatory microRNAs (miRNAs) have been shown to decrease inflammatory cytokines in preclinical models of PF. These carriers not only transport medicines to target areas but also lead to changes in immunological function, decreased inflammation, and tissue repair [90, 91]. According to a prior study [92], exosomes carrying anti-inflammatory miRNA significantly decrease inflammatory cytokine levels in COPD models. Therefore, exosomes can be used in therapeutic treatment of lung fibrosis. Another unique method involves coating nanoparticles with cell membranes. In these nanoparticles, membranes found on cancer cells or immune cells are used to achieve localization and evade the immune response [93–95]. Nanoparticles coated with cancer cell membranes can mimic the natural “homing” behavior of tumor cells and consequently deliver drugs specifically to fibrotic or metastatic lung tissues [96].

Enhancing pulmonary drug delivery

Advanced delivery systems use several strategies to enhance drug delivery and therapeutic efficacy. Nanoparticles use the enhanced permeability and retention (EPR) effect to accumulate in fibrotic tissues. Active targeting involves functionalization of nanoparticles with ligands such as antibodies or peptides that bind receptors that are overexpressed in fibrotic tissues, such as $\alpha\text{v}\beta 6$ integrins [97–99]. Nanoparticles that target $\alpha\text{v}\beta 6$ integrins, receptors associated with fibrosis, have shown enhanced localization and therapeutic effectiveness. Hydrogels provide controlled and prolonged drug release ensuring therapeutic efficacy over extended periods. This aspect is particularly beneficial for chronic conditions such as PF, in which long-term treatment is required [100, 101]. Oxygen-releasing hydrogels progressively release oxygen, thereby addressing hypoxia-related pulmonary disorders. Biological carriers such as exosomes interact with

immune cells, such as macrophages and dendritic cells, and create an anti-inflammatory microenvironment. This dual role of drug delivery and immune modulation is critical in addressing the complex pathophysiology of PF [85, 102].

Conventional pulmonary medication administration techniques have many limitations. First, they protect therapeutic molecules against enzymatic breakdown and mucociliary clearance and consequently increase drug bioavailability [103, 104]. Second, they prevent systemic adverse effects and achieve focused medication delivery to sites of illness. Although corticosteroids have been optimized to reduce systemic side effects, their efficacy as targeted therapies for inflamed lung regions remains limited [105, 106]. These methods also help patients adhere to medication regimens by decreasing the number of doses. Sustained-release hydrogels provide therapeutic benefits over weeks by reducing the need for frequent drug administration and minimizing systemic side effects [107, 108]. Furthermore, sophisticated systems exhibit versatility in accommodating diverse therapeutic agents, including small molecules, biologics, and nucleic acids. These delivery systems can be tailored to specific medical situations. Hydrogels engineered to replicate the biomechanical characteristics of fibrotic lungs have shown improved therapeutic effectiveness in preclinical studies [109, 110].

Biomaterials play critical roles in addressing the unique challenges of lung fibrosis. Their abilities to mimic the ECM, deliver drugs precisely, and modulate the fibrotic microenvironment make them invaluable in PF treatment. Decellularized scaffolds derived from donor lungs provide a natural ECM framework that can be repopulated with patient-derived cells to promote lung regeneration and decrease fibrosis [111]. Electrospun nanofibers can be engineered to mimic the native lung structure, and support cell growth and tissue repair [111]. Stimulus-responsive biomaterials, which release drugs in response to specific biochemical cues, are being developed to target fibrotic tissues more effectively [112].

Nanotechnology-based DDSs, which use various nanomaterials to enhance drug targeting and release, have emerged as promising alternatives to conventional systemic drug administration. These nanomaterials—including liposomes, polymeric nanoparticles, dendrimers, and solid lipid nanoparticles—offer advantages such as improved bioavailability, controlled drug release, and decreased systemic toxicity (Table 2).

Liposomal formulations have been widely studied because of their ability to encapsulate both hydrophilic and hydrophobic antifibrotic agents, thus ensuring targeted delivery to lung tissue while minimizing off-target effects [113, 114]. Similarly, polymeric nanoparticles, particularly those based on biodegradable polymers such as PLGA, provide sustained drug release and improved stability, which can enhance the therapeutic efficacy of drugs such as pirfenidone and nintedanib [115–117]. Metallic nanoparticles and mesoporous silica nanoparticles also have potential because their unique surface properties facilitate targeted drug transport and controlled release [118, 119]. These nanotechnology-based approaches are particularly relevant for PF treatment, because they enable localized drug deposition in

Table 2 Overview of Various Nanomaterials, and their Advantages, Mechanisms of Action, and Applications in Targeted Drug Delivery Systems

Nanomaterial	Examples	Advantages	Mechanism of Action	Applications in Drug Delivery
Liposomes	Doxil (liposomal doxorubicin)	Biocompatible, low toxicity, can encapsulate hydrophilic and hydrophobic drugs	Lipid bilayer encapsulation of drug and release at target sites	Cancer therapy, vaccines, gene therapy
Polymeric nanoparticles	PLGA (poly(lactic-co-glycolic acid))	Biodegradable, controlled drug release	Encapsulation or surface attachment of drugs	Anticancer drugs, antibiotics, anti-inflammatory agents
Dendrimers	PAMAM (poly(amidoamine))	High surface area for drug attachment, precise control of structure	Encapsulation or covalent attachment to functional groups	Gene delivery, chemotherapy, imaging agents
Metallic nanoparticles	Gold, silver, iron oxide	Unique optical and magnetic properties, high stability	Surface functionalization for drug loading and release	Targeted cancer therapy, biosensors, imaging
Carbon-based nanomaterials	Carbon nanotubes, graphene	High drug loading capacity, excellent thermal conductivity	Adsorption of drugs onto the surface or within the structure	Anticancer therapy, gene delivery, photothermal therapy
Solid lipid nanoparticles	Compritol 888, stearic acid	Biocompatible, scalable production	Lipid matrix encapsulates drugs	Antiviral drugs, anticancer drugs, brain-targeted delivery
Nanogels	Hydrogel nanoparticles	High water content, flexible drug release profiles	Drug encapsulation within a gel-like network	Protein and peptide delivery, cancer therapy
Mesoporous silica nanoparticles	SBA-15, MCM-41	High surface area, tunable pore size	Adsorption or encapsulation within silica pores	Drug delivery for anticancer and antiviral therapies

the lungs, thus overcoming challenges associated with systemic administration [120]. By enhancing drug retention in fibrotic lung tissue and decreasing the frequency of dosing, these DDSs have potential to improve patient adherence and overall treatment outcomes.

Models for PF

Clinical trials in humans, including phase II and III trials, to date have indicated failure of most biologics and medications tested for PF. Some well-established *in vivo* or *in vitro* 2D or 3D models used to evaluate PF, including asbestos, bleomycin, silica, age-associated and cytokine overexpression models, may have flaws that have not yet been fully discovered [121, 122]. Hence, the critical events that initiate the aberrant proliferation of fibroblasts, tissue fibrosis, and abnormal repair of epithelial cells must crucially be understood through evaluation of the specific molecular pathways induced by PF [123–125]. Disease models play essential roles in PF pathophysiology research and drug screening. Below, we examine several *in vivo* and *in vitro* models that have been used to disease progression in PF (Figure 3).

In vitro models

Various cell types contribute to fibrosis progression, including fibroblasts, and epithelial and immunological cells. The most frequently used cell lines are A549, IMR-90, MRC-5, and NCI-H441 [123, 126]. These cells are inherently immortalized and cannot exhibit persistent phenotypic alterations akin to those of human lung cells. Other cell types are sourced from human donors. Lung fibroblasts are used to precisely examine the pathological alterations in PF, in contrast to immortalized cells [127]. Moreover, 3D models

duplicate the lung microenvironment more effectively than 2D models, by simulating cell-to-cell and cell-to-matrix interactions, as well as the stiffness and structure of the extracellular matrix [128]. In addition, 3D models can provide insights into chemotaxis, migration, integrin adhesion in all three dimensions, cellular traction, soluble growth factors, and the formation of air-liquid interface epithelial cells, thus enabling more accurate simulation of the conditions *in vivo* [129, 130].

In vivo models

In vivo animal models in rats or mice are used to imitate the progressive and chronic nature of PF and to duplicate real-time alterations in the internal environment of the lungs throughout PF advancement. These models are crucial for assessing disease progression and evaluating pharmacological interventions for PF therapy [131, 132]. Nonetheless, the physiological and internal environments of these animals with PF illness differ from the human physiological milieu, and consequently create hurdles for the clinical translation of any treatment approach to first-in-human trials [133]. Furthermore, PF is cured or reversed over time in rats, in contrast to the persistent, non-resolving fibrotic process seen in humans [134]. The development of an efficient delivery system relies on choosing the proper *in vivo* mouse model for pulmonary formulation, by considering the similarities and differences between murine and human lungs [135, 136]. The pulmonary circulation receives blood from the right ventricle of the heart and supplies the lobes of lung parenchyma, which include branches of bronchioles, to the lungs in both humans and mice [137, 138]. In contrast to humans, who have two lobes on each side of the lung, mice have four lobes on the right side and one on the left [139]. Mice have monopodial bronchial branching and lack cartilage, whereas humans have dichotomous branching

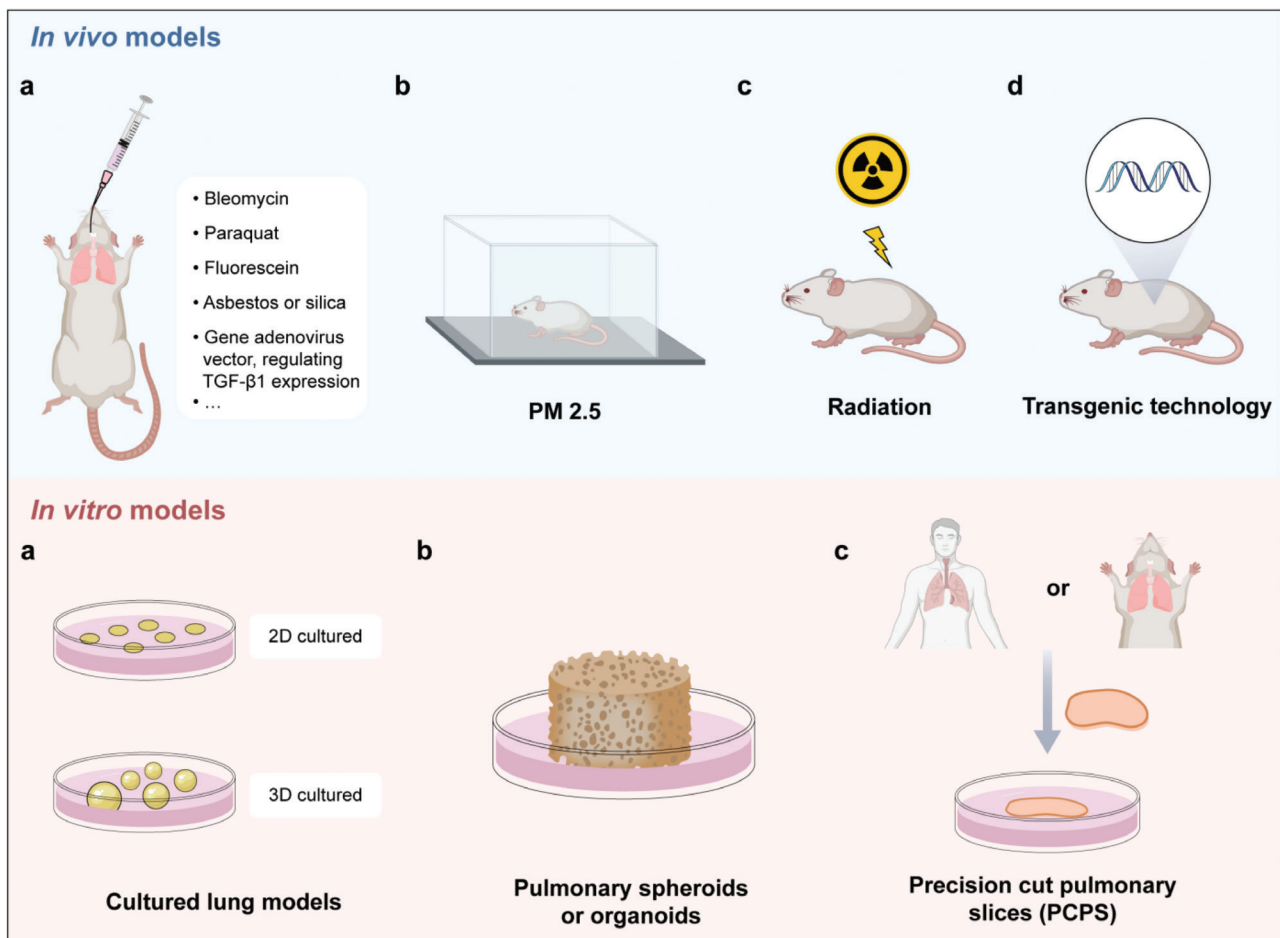


Figure 3 Models of PF. *In vivo* models treated with medicine, PM_{2.5}, radiation, and transgene technology. *In vitro* models treated with cell cultured pulmonary spheroids or organoids and PCPS.

and possess cartilage. The tracheal epithelium thickness is 11–14 μm in mice and 50–100 μm in humans [140, 141]. Variations in lung morphology, including the number of lobes, branching patterns, and cartilage distribution in the airways, are evident across various species. The lungs of mice and humans range in size, including variations in airway diameter and alveolar dimensions, as well as breathing rate [142]. In mice, the terminal bronchiole often connects directly to an alveolar duct, whereas in humans, respiratory bronchioles open into the alveolar duct [143, 144]. The tracheobronchial pseudostratified epithelium in mice comprises club cells (49%), ciliated cells (39%), and basal cells (10%), while in humans, it consists of ciliated cells (49%), goblet cells (9%), and basal cells (33%), with minor cell types (e.g., neuroendocrine or brush cells) accounting for the remaining proportions [145].

Bleomycin causes a transient fibrotic response in animal models of PF; this reaction is marked by oxidative stress and is eventually resolved by healing and regeneration [146]. In contrast, lung fibrosis develops slowly from days to months in humans, does not include regeneration of lung cells, and may last for a long time after treatment is stopped [147]. Human bleomycin and animal models have an unclear etiology, because bleomycin models in mice do not capture

cellular connections, genetic vulnerability, and immune system function [148].

Mutant surfactant Protein C murine model closely recapitulating PF

Surfactant dysfunction causes respiratory discomfort during the active production of TGF- β 1 in early fibrosis, thus resulting in a lack of remodeling in the disease's first phase [2, 147, 149–151]. Active TGF- β 1 may diminish the functionality of biophysically active surfactant protein C (SFTPC) and induce misfolding in mutant proteins inside alveolar epithelial type II cells by decreasing the activity of thyroid transcription factor-1 in the nucleus [152, 153]. This response leads to a complete lack of mature SFTPC and triggers PF. One study [154] has reported an SFTPC model caused by the virally mediated introduction of a mutant TGF- β 1 gene by intratracheal instillation, and indicated elevated collagen fiber levels inside interalveolar septal walls and diminished surface area of the apical plasma membrane by the 14th day. AE2 cells were identified between the stacked septal walls, and were visualized by microscopy and found to be encased by epithelial basal lamina [155, 156]. Whether the AE2

cells were responsible for surfactant metabolism because of the absence of an observable interface with the airspace remained unclear [157]. Typically, elevated surface tension at the alveolar air-liquid interface and the impairment of AE2 functionality are the first changes associated with TGF- β 1 gene transfer and may also be observed in other PF models [158, 159].

In human PF, the collapsibility of distal airspaces in early stages may indicate that dysregulation of these airspaces is associated with remodeling [160–164]. Microatelectasis has been detected in human PF lungs without fibrotic remodeling and investigated with micro-computed tomography [165–167]. Consequently, alveolar collapse is a significant occurrence that might result in fibrotic remodeling and elucidate the mesenchymal transition from lung inflammation to lung fibrosis. Previous studies have examined end-inspiratory and end-expiratory HRCT images of human fibrotic lungs, and observed that abnormalities were pronounced only during end-expiratory situations but remained unchanged during end-inspiratory conditions [168, 169]. These data indicate that the loss of air at end-expiration is attributable to the collapsibility of distal airspaces in areas that have not yet undergone remodeling, and that the collapsibility resulting from the lack of SFTPC precedes the remodeling process [170, 171]. Additionally, significant impairment in surfactant function is a common characteristic in individuals with PF [172]. These studies examined the replication of SFTPC murine models in human PF through the following means [173]: (1) stabilization of distal airspaces during the early fibrotic phase, decreased pro-fibrotic septal wall remodeling, and induction of AE2 abnormalities at a later stage [174], and (2) evaluation of the efficacy of surfactant replacement therapy in stabilizing distal airspaces during the early transition phase. Elevated surface tension and alveolar collapsibility have been demonstrated to precipitate lung damage and pro-fibrotic remodeling in the TGF- β 1 driven SFTPC mouse model and in human PF [175, 176]. Nonetheless, animal models remain essential for investigating PF and aid in evaluating specific signal transduction pathways, or physiological structures, as well as in developing efficient drug delivery devices [177].

Mechanisms and barriers in pulmonary drug delivery

PF is a progressive and life-threatening disease that poses major challenges to effective medication delivery, because of structural or metabolic alterations in pulmonary tissue. Excessive ECM deposition, compromised epithelial/endothelial barrier integrity, and persistent inflammation represent critical barriers to effective drug delivery in fibrotic tissues [178, 179]. Nevertheless, current advancements in nanotechnology and DDSs indicate substantial room for improvement in the results [180]. The molecular and anatomical challenges presented by the disease, along with strategies to overcome them, and the methods of drug delivery appropriate for PF have been described previously [80].

Biological and structural barriers in PF

Intense accumulation of collagen, fibronectin, and elastin in areas of alveolar enlargement results in wall thickening and rigidity, and decreases the penetration and diffusion of drugs. This effect has been extensively recorded. For example, Gonzalez et al. (2024) demonstrated that these structural changes impede drug penetration and alter lung physiology by reducing tissue compliance (stretchability) and elasticity, thereby impairing respiratory function [55]. The ECM poses a mechanical obstacle via its dense crosslinked network, which prevents the delivery of therapeutic agents, particularly macromolecules and nanoparticles [181].

Epithelial and endothelial dysfunction exacerbates the challenges of medication delivery. Despite preserving the lung's protective barrier, tight connections in epithelial cells limit paracellular drug transport [182]. In fibrotic areas, epithelial cells often sustain damage, and tight junctions may become dysregulated, thereby introducing variability in medication distribution [183]. Capillary rarefaction, a characteristic of PF, impairs normal circulatory networks, diminishes blood flow to fibrotic areas, and restricts the effectiveness of systemically delivered medications [184]. A prior study [185] has shown that vascular remodeling and hypoxia in fibrotic tissues intensify medication delivery difficulties, because hypoxic environments modify drug metabolism and efficacy.

Activated fibroblasts differentiate into myofibroblasts, which drive pathological fibrosis by overproducing ECM proteins, thereby increasing tissue stiffness and disrupting lung architecture [186, 187]. These cells also secrete profibrotic cytokines such as TGF- β , creating a fibrotic microenvironment that impairs drug penetration and efficacy [188]. These difficulties are exacerbated under chronic inflammation, which is characterized by macrophage polarization and cytokine secretion. In the context of fibrotic lungs, one study [187] has shown that such an inflammatory environment decreases the stability and bioavailability of medications, thus requiring highly sophisticated delivery strategies.

Approaches to overcome delivery challenges

To overcome the major difficulties in PF, researchers are developing new drug delivery methods. Overcoming biological and structural obstacles is an essential part of nanotechnology. One current DDS for treatment of PF is lipid nanoparticles (LNPs) [53, 189]. As they protect pharmaceuticals from enzymatic destruction, LNPs also increase the solubility, stability, and bioavailability of medicinal substances [190, 191]. In a thorough evaluation of LNPs, one study [192] has demonstrated the ability of LNPs to deliver antifibrotic drugs, such as pirfenidone and nintedanib, directly to fibrotic lungs. Drug delivery is improved by combining PEG coatings on the surfaces of lithium nanoparticles to achieve immune recognition, thereby increasing the circulation time of the medication [193, 194]. A new approach involves peptide based controlled delivery systems. The use

of shuttle peptides enhance intracellular drug delivery by enabling therapeutics to traverse mucus layers and penetrate epithelial barriers. For instance, a study [195] showed that these peptides facilitate the transport of phosphorodiamidate morpholino oligonucleotides in preclinical PF models, improving therapeutic access to fibrotic lung tissue. These peptides successfully penetrate the dense ECM and stimulate endocytosis, thus increasing the bioavailability of the delivered drug [196].

Stimulus responsive nanoparticles are highly appropriate for the fibrotic lung microenvironment. One study [197] has constructed redox-responsive nanoparticles that are encapsulated in neutrophil membranes and escape immune clearance while specifically targeting fibrotic areas. In preclinical experiments, these nanoparticles have been found to deliver their therapeutic payload in response to the type of oxidative stress in fibrotic tissues, and therefore achieve specific targeting and therapeutic efficacy [198]. Consequently, attention has been paid to mesoporous silica nanoparticles (MSNs), which provide high drug loading capacity and tunable release. MSNs can be modified with ligands that target fibrotic tissue indicators, such as integrins, to enable site-specific delivery [199, 200]. One study [201] using MSNs to deliver small interfering RNAs targeting TGF- β has observed substantially decreased ECM deposition and myofibroblast activation in murine models of PF.

Another promising approach is combination medicines including several different delivery modalities. For example, the combination of LNPs with stimuli-responsive systems capitalizes on the advantages of both platforms in overcoming fibrosis-related challenges [202, 203]. In addition, preclinical research has shown that multifunctional nanoparticles that can simultaneously deliver anti-inflammatory and anti-fibrotic drugs provide synergistic benefits [204].

Modes of administration and their applications

The choice of administration route should be considered to achieve maximal therapeutic effect in the case of PF [2]. Delivery methods (e.g., inhalation, systemic injections, or combined approaches) exhibit distinct advantages depending on the drug's physicochemical properties and its ability to achieve localized targeting within pulmonary or systemic compartments [205, 206]. Inhalation delivery devices are preferred in the management of PF, because they deliver medication directly to the lungs and avoid the systemic route [207, 208]. Aerosolized nanoparticle formulations have been demonstrated to enhance medication retention while minimizing systemic side effects [209], in which medication retention was improved and the systemic adverse effects were decreased. Initial case control clinical trials have demonstrated that liposomes containing formulations of corticosteroids and antifibrotic drugs offer improved pharmacokinetics and performance [210].

Nanocarriers may be administered through intravenous injection for systemic administration of complex nanomedicines. Drug delivery to unreachable fibrotic areas can be achieved in a less resource-intensive manner through this

route, while ensuring uniform drug distribution throughout the pulmonary region [211, 212]. In a recent study [213], folate-targeted liposomal versions of paclitaxel showed prolonged residence times in fibrotic lung parenchyma. These formulations showed diminished off target effects, owing to the high selectivity of the receptors in lung tissues. Systemic and localized administration modalities in combination medicines have revealed enhanced therapeutic effects. One study [214] has established a thermochemotherapy hybrid system comprising gold nanorods combined with platinum prodrugs. The synthesized gold nanorods elicited localized heat under irradiation with near infrared light, thus facilitating the penetration of medications to the fibrotic tissues [215, 216]. This two-in-one device has been found to decrease ECM deposition and improve lung function in experimental models. Inhalation and systemic combined delivery systems are currently under study. These methods are aimed at exploiting the advantages of both pathways: localized administration for prompt therapeutic effects and systemic administration for prolonged efficacy [217–219]. These techniques are particularly pertinent in addressing the progressive characteristics of PF, in which both localized and systemic mechanisms play roles in disease progression [2].

Potential therapeutic approaches for PF in clinical phases

In recent decades, clinical studies on PF have markedly increased in quantity, scale, and quality (Figure 4). The decade from 2000 to 2010 offered essential insights into the condition, although numerous experiments produced inadequate outcomes. These investigations provided important findings regarding PF pathophysiology and its clinical development, particularly through well-defined patient cohorts. The PANTHER study underscored the possible adverse effects of anti-inflammatory and immunosuppressive medicines, and led to cessation of research on alternative therapy classes, including anticoagulants, endothelin inhibitors, and anti-phosphodiesterase agents [112, 220]. The INPULSIS and ASCEND studies achieved significant advancements culminating in the approval of the inaugural anti-fibrotic medications, pirfenidone and nintedanib [221]. These trials underscored the significance of including patients with mild-to-moderate PF and used forced vital capacity as a key outcome [222]. Nonetheless, neither pirfenidone nor nintedanib can cure PF or impede disease progression in most patients, and both are associated with considerable adverse consequences. Consequently, novel trials investigating targeted medicines and combination therapies have been initiated, to attain safer and more synergistic results [223].

Considering the successful phase II trials for pirfenidone and nintedanib, which are currently in phase III, researchers have shifted focus to innovative medicines including GLPG-1690, pamrevlumab, and pentraxin [224]. These medications, when used alongside current anti-fibrotic treatments, have shown potential, thus indicating the strength of the study methods

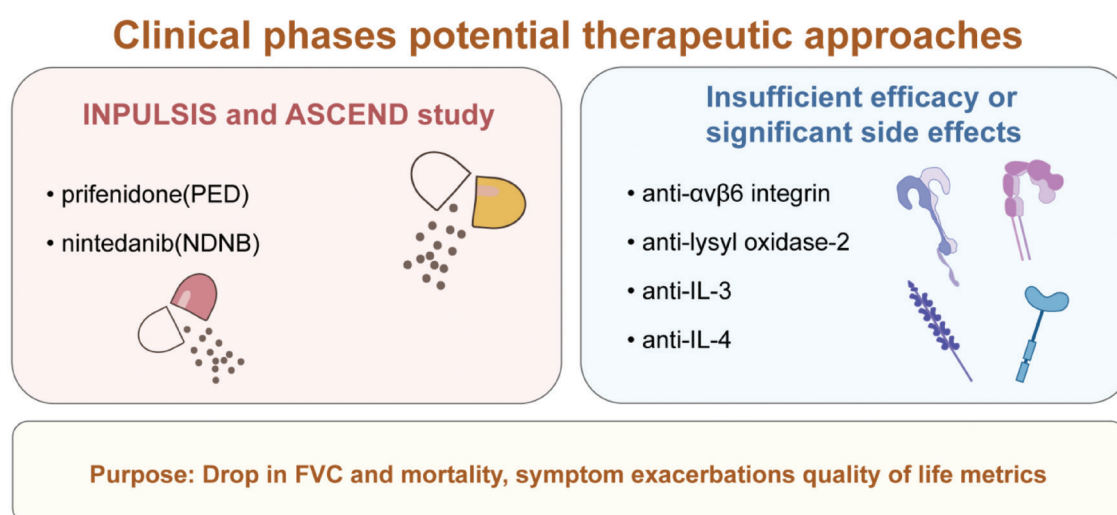


Figure 4 Clinical phases of potential therapeutic approaches, demonstrating effective research and ineffective research, and prospects for future research.

[223, 225]. These substances are currently in the concluding phases of PF research, and may transform PF management. Notwithstanding these developments, other phase II trials aimed at various molecular pathways have been terminated because of either insufficient efficacy or significant adverse effects. Examples included antibodies directed against ECM constituents (e.g., anti- α v β 6 integrin), anti-lysyl oxidase-2, anti-IL-13, and anti-IL-4. The intricacies of PF remain only partially elucidated, and novel therapies frequently lack the requisite validation for effective trial formulation. To enhance trial outcomes, innovative endpoints should incorporate decreased forced vital capacity alongside mortality, symptom exacerbations, and quality-of-life metrics. Moreover, quantitative assessment of PF through CT imaging may advance understanding of the fibrotic pulmonary milieu [223].

Challenges and future perspectives

Key challenges in designing and implementing targeted drug delivery systems

The design and deployment of TDDSs for PF encounter many challenges, owing to the intricacy of the illness and the pulmonary milieu. These obstacles can be categorized into receptor-, ligand-, carrier-, and clinical translation-specific concerns, each of which requires creative strategies and further technical progress [226–228].

Challenges with receptors

A major challenge in the treatment of PF is identifying the appropriate receptors against which to target the therapy. PF involves a dynamic cellular milieu comprising a variety of

receptors, including integrins, TGF- β receptors, and fibroblast activation protein, which are important in fibrosis [229, 230]. However, heterogeneity in receptor expression among cell groups and fibrotic areas has prevented progress in targeted therapeutics [231, 232]. In fact, α v β 6 integrins are overexpressed in fibrotic tissues but may be crowded out by deposition of thick ECM, thus rendering nanoparticle based or ligand mediated delivery methods ineffective [233, 234].

Another significant problem is receptor shedding, which occurs when soluble receptor versions are released into the extracellular environment. This phenomenon hinders effective receptor targeting. One study [235] has indicated that shedding of cytokine receptors, such as TGF- β receptor II, under fibrotic circumstances limits the efficiency of ligand-based delivery systems. These restrictions highlight the need to increase the accuracy of receptor mapping and to dynamically monitor the availability of receptors in fibrotic lungs [236, 237]. Another key issue is receptor shedding, where soluble forms of receptors (e.g., TGF- β receptor II) are released into the extracellular environment. This phenomenon disrupts ligand-receptor binding and reduces the efficacy of receptor-targeted therapies such as ligand-based delivery systems [238, 239]. To address this, advancements in dynamic receptor mapping and real-time monitoring of receptor availability are essential to refine targeting strategies and improve therapeutic precision.

Ligand-specific challenges

The design of TDDSs for PF is another consideration that complicates ligand selection. First, the choice of ligand requires high selectivity toward a target receptor and should not interact with other receptors [182, 183]. Moreover, conjugation of ligands to drug carriers may involve sophisticated chemical procedures, such as use of linkers to unload drugs in the region of interest [240, 241]. However, these linkers must achieve stability within the circulation and be rapidly released at sites of action. An inhaling device needs stimulus

responsive linkers for mild drug release under the acid and protease rich environment of PF [242, 243]. Ligands targeting growth factors or matrix-related proteins also face limitations, owing to their non-specific binding to multiple cell types within the lungs. For example, ligands targeting PDGF receptors might affect vascular cells and lead to off-target effects. Consequently, multifunctional ligands capable of simultaneous targeting and therapeutic action must be designed [244, 245].

Carrier-specific challenges

Known challenges regarding carriers include the choice of the proper nanoparticle type and the improvement of their properties. Challenges in PF include consideration of increased deposition of ECM, greater tissue stiffening, and decreased alveolar patterning [246, 247]. These challenges are met by carriers that can penetrate thick fibrotic tissues and sustain the release of therapeutic drugs. Nanoparticle based carriers, including polymeric and lipid systems, are devices of interest but present several inherent issues [248, 249], including particle size particles, charge and surface hydrophobicity. Particles with diameters less than 100 nm have high penetration potential in fibrotic tissue; however, extremely small particles can be easily cleared by alveolar macrophages [250, 251]. PEG or other hydrophilic polymers can be used for surface modification. However, this modification may further prolong circulation duration at the cost of targeted efficacy [252]. Nevertheless, issues concerning biocompatibility and toxicity are paramount. Most lipid-based carriers are well tolerated, but some inorganic carriers, such as silica nanoparticles, can stimulate inflammatory reactions or disrupt normal pulmonary processes [253]. Furthermore, developing nanocarriers for therapeutic applications faces increasing production constraints coupled with a need to maintain consistent high quality [254].

Clinical translation barriers

Translation of TDDSs for PF into practice involves several difficulties. The passive targeting incorporated within DDSs, particularly the EPR effect, has diminished effectiveness in PF [53, 255], thus constraining nanoparticle buildup, particularly in fibrotic tissues requiring enhanced targeting approaches that involve ligand-receptor interactions [256]. The tumor heterogeneity commonly encountered in oncology is also evident in PF, because of differences in the composition and cellular organization of fibrotic lesions [257, 258]. Fibrotic lesions rarely exist as isolated replacements of normal lung tissue; their intermixed nature with healthy parenchyma poses significant challenges for selective therapeutic targeting. This heterogeneity poses substantial challenges in dose optimization and increases the risk of adverse effects to other target sites [259]. Regulatory hurdles and scalability also impede the clinical translation of nanomedicines for PF [260, 261]. Manufacturing of targeted delivery systems requires stringent quality control and reproducibility, particularly for nanocarriers with complex surface

modifications. Furthermore, long-term toxicity studies are needed to assess the safety of these systems, particularly because fibrotic diseases often require prolonged treatment [262].

Opportunities for clinical translation and precision medicine

A revolutionary change in the treatment of PF has resulted from the incorporation of precision medicine and its clinical translation. Progressive PF pathogenesis can be variable, and traditional therapies may fail to provide adequate relief [263, 264]. TDDSs, however, rely on precision medicine principles to enhance treatment results [265]. Developments in nanotechnology, biomarker identification, and tailored treatment platforms are bridging the gap between laboratory research and real world clinical use [266, 267]. A critical frontier in PF research involves advancing both the mechanistic understanding and structural complexity of engineered drug carriers to optimize their clinical translation. Mechanisms have been developed to enable liposomes and polymeric systems to penetrate fibrotic tissues and deliver therapeutic medicine to these sites [268].

Traditional treatments usually fail because of the biological barriers through which these carriers must pass, including those contributing to increased ECM deposition [269]. Pirfenidone, an anti-fibrotic drug, may be more effectively delivered to fibrotic tissues after it is encapsulated in lipid-based nanoparticles, owing to increased bioavailability [270, 271]. Likewise, stimuli-responsive polymeric nanoparticles release therapeutic agents in response to specific microenvironmental cues (e.g., pH, enzymes, or redox gradients) inherent to fibrotic tissues, enabling precise drug activation at disease sites [272, 273]. This may involve responding to biochemical signals such as acid conditions or increased enzymatic activity at fibrotic lesions. For clinical translation, these systems are undergoing refinement via scalable manufacturing technologies, such as microfluidic synthesis, as well as thorough regulatory assessments to ensure both safety and effectiveness [274].

To further enhance the clinical utility of these technologies, precision medicine tailors therapeutic strategies to individual patient needs, enabling personalized treatment development that addresses specific disease manifestations [275, 276]. One leading strategy is the use of biomarkers for patient stratification. Structural and functional biomarkers including circulating microRNAs, matrix metalloproteinases, and serum surfactant proteins not only support the identification of subtypes of diseases but also predict treatment response [277, 278]. Such insights can be used to guide the selection of target medicines according to the distinctive molecular and clinical features of individual patients. Second, genomic and proteomic studies have provided a partial picture of the intracellular signaling events that underlie fibrosis. For example, the TGF- β signaling pathway, which was discovered recently, can be targeted with enhanced delivery

systems. Another example is precise molecular targeting of the disease-specific process by using nanoparticles to selectively deliver TGF- β inhibitors to fibrotic tissue [279].

Clinical translation may also benefit from theranostics, a platform that combines diagnostic and therapeutic capabilities. Drug distribution and treatment response can be monitored in real time with theranostic nanoparticles combining imaging agents with therapeutic payloads [280, 281]. Clinicians may optimize the results and minimize risks by dynamically adjusting treatment plans on the basis of this dual feature. The use of theranostics in PF may be particularly useful for monitoring disease course and determining the effectiveness of antifibrotic treatments. Nanoparticles containing imaging contrast agents and antifibrotic medications have shown encouraging outcomes in preclinical models, thereby highlighting the practicality of such systems [202].

Another potential application of exosome based delivery systems in PF is state focused precision medicine. Exosomes are biological membranes that can be used to deliver biologics including anti-inflammatory cytokines or small interfering RNA [282]. They are intrinsically biocompatible and can avoid immune recognition, and consequently are ideal for targeted therapy. MSC-derived exosomes have been reported to alleviate lung injury and to decrease fibrotic activity in animal models [283]. These findings further support the prospects summarized in the previous section to potentially achieve personalized exosome-based treatments for PF [284].

Several obstacles remain in the use of these technologies in clinical practice, despite recent achievements. Targeting medication delivery systems is complicated, owing to the variety of fibrotic lesions both within and across individuals. The nanoparticles show targeting ability at cancer tumors via endothelial EPR; however, EPR is not substantial in fibrotic areas [285]. Therefore, receptor-ligand interactions must be highly selective, and guided through active targeting mechanisms such as ligand mediated delivery. A significant challenge is the heterogeneity in receptor expression and receptor availability in the fibrotic lungs. This challenge can be addressed through precision medicine methods involving real-time observation of patients and dynamic adjustment of the treatments on the basis of data for each individual [286].

Nanorobotics and bioengineered nanoparticles are two examples of emerging technologies that may provide further opportunities for creativity. By bypassing endocytosis and passive diffusion, nanorobots fitted with sensors and actuators might explore fibrotic tissues and administer medications with unmatched accuracy [285, 287]. Another strategy for improving the targeted specificity and evading immune detection is the use of bioengineered nanoparticles that imitate the natural cellular architecture [288]. Many current obstacles in PF medication distribution may be solved with these next-generation technologies [289].

Precision medicine is frequently based on AI and data analytics. We can leverage AI-driven algorithms to analyze genomic, proteomic, and clinical datasets, predicting patient-specific treatment efficacy, biomarker-driven responses, and resistance mechanisms [290]. New patient perspectives within the framework of illness development and treatment response may inform treatment plans tailored to patients' needs. AI can be used for nanoparticle design

optimization to select the optimal size, charge, and surface modification combinations for individual patient profiles [291, 292]. Finally, progress in PF therapy was previously impossible before clinical translation and precision medicine were united. Researchers and physicians are creating more precise and efficient treatments using theranostic platforms, biomarker-driven stratification, enhanced drug carriers, and new technologies [291, 293]. Innovation and interdisciplinary cooperation should advance this area, despite persistent problems including heterogeneity, regulatory roadblocks, and scalability. Precision medicine's ability to provide efficient and personalized treatment options for patients with PF bodes well for long-term health and well-being [294].

Future directions in biomaterials research for PF

PF is a persistent ailment that deteriorates with time and poses a substantial threat to the patient's vitality. In addition, it substantially influences quality of life and respiratory system functioning. The mechanism underlying the onset of this sickness has not yet been identified, although many studies have examined the signaling pathways and molecular mechanisms of PF. Therefore, developing medications for PF is difficult. The only pharmaceuticals currently available are pirfenidone and nintedanib. However, both target different pathways, and their exact mechanisms are unknown. They also elicit various adverse effects over the duration of long-term therapy, and they cannot reverse structural abnormalities such as fibrosis. Pulmonary rehabilitation exercises, hormonal and immunosuppressive medication, oxygen inhalation, and other clinical therapy modalities are used as supplementary programs that are not effective alone [295]. Therefore, improving DDSs is necessary to optimize treatment plans when progress in target and mechanism research is not imminent.

An effective method is improving the dose forms of nintedanib and pirfenidone. Drugs may be more effectively delivered and used for longer periods via gradual and controlled release when the administration route is changed or when additional active ingredients are co-loaded to provide synergistic therapeutic effects. A variety of medications target different mechanisms in the treatment of PF, including hormone therapies, gene drugs, and small-molecule drugs [296]. The lack of an adequate model to mimic the actual clinical disease is another factor contributing to the slow advancement of PF research. The clinical translation of medications with promising findings in animal research may be challenging, because commonly used animal models of PF, including bleomycin-induced PF in mice, do not reflect human pathogenic features and disease development. Consequently, several *in vitro* models have been developed by researchers. PF disease models are being enhanced by the development of new approaches such as organoid building, PCPSs, 3D printing, lung chips, and more traditional 2D and 3D tissue culture techniques [297]. Current technological limitations prevent the pathophysiological features of PF from being fully mimicked *in vitro*. Therefore, animal models remain the primary focus of drug delivery and screening research. Researchers continue to work to overcome

the limitations of animal PF models, such as differences in human and mouse disease progression [2, 298].

In conclusion, several obstacles must be overcome in PF drug delivery systems. Given the multifactorial nature of PF pathogenesis, future studies may focus on medication co-delivery methods for multi-target synergistic therapy, because treatments that target a single signaling pathway or factor are often insufficient. Furthermore, the clinical stages of PF remain unclear. However, as the illness advances, its pathophysiology changes significantly, thus leading to fewer successful treatment plans. Therefore, appropriate identification of PF is critical. Another strategy for designing such delivery systems is to locally target pharmacological agents to specific pathogenic cells (e.g., macrophages and fibroblasts) driving pulmonary fibrosis progression [299]. In use of biological agents, antibodies and proteins, DNA and gene therapy, as well as other systems, purposefully choosing the proper medicine is critical. To design better drugs and DDSs, and to further improve upon medication delivery methods, better understanding of the specific causes is required to derive better targets in drug development. Therefore, accurate illness models must be built to study the mechanism and assess medications for PF treatment *in vitro*.

Declarations

Data availability statement

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

Author contributions

Haoguang Li conceptualized and designed the study. Jinsha Liu and Zifeng Pan contributed to drafting the manuscript. Haoguang Li and Arshma Khan revised the manuscript. All authors have read and approved the final version of the manuscript.

Conflict of interest

The authors declare that there are no conflicts of interest.

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