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Advancements in Pulmonary Fibrosis Research: Exploring Mouse Models and the Role of Traditional Chinese Medicine in Pathogenesis and Therapy (2015-2025)

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Abstract: ***Pulmonary fibrosis, particularly idiopathic pulmonary fibrosis (IPF), is a chronic progressive lung disease with an extremely poor prognosis and limited treatment options. Although two antifibrotic drugs have been clinically approved, they can only slow disease progression and fail to completely halt fibrosis development. In recent years, significant progress has been made in understanding the pathogenesis and potential treatments of pulmonary fibrosis through animal models, especially murine models. However, existing mouse models still fail to fully replicate the pathological characteristics of human IPF, and many interventions effective in mice have not been successfully translated to clinical practice. Therefore, there is an urgent need to explore novel therapeutic approaches. Traditional Chinese Medicine (TCM), with its multi-component and multi-target characteristics, demonstrates unique advantages in the prevention and treatment of pulmonary fibrosis. This review summarizes research advances in pulmonary fibrosis mouse models from 2015-2025 and explores the potential of TCM interventions in pulmonary fibrosis treatment based on modern TCM theories. The article focuses on analyzing pathological mechanisms, common murine models, signaling pathways, and the latest TCM intervention research findings, aiming to provide new perspectives and approaches for clinical pulmonary fibrosis treatment.***

Keywords: Pulmonary fibrosis, Murine model, Traditional Chinese Medicine**.**

1. Introduction

Pulmonary fibrosis, represented by idiopathic pulmonary fibrosis (IPF), is a type of chronic progressive pulmonary disease with an extremely poor prognosis and limited treatment options. Currently, only two antifibrotic drugs, pirfenidone and nintedanib, have been approved for clinical use. While they can delay disease progression, they are unable to halt fibrosis development [1]. Over the past decade, extensive research based on animal models (particularly mice) has achieved significant progress in elucidating the pathogenesis of pulmonary fibrosis and exploring novel therapies. However, the understanding of IPF pathophysiology remains incomplete, and there are limitations in translating preclinical mouse models to human disease: many interventions that demonstrated antifibrotic effects in mice (such as the antibody simtuzumab, the tyrosine kinase inhibitor imatinib, and the anti-PDGF monoclonal antibody pamrevlumab) failed to improve patient outcomes in clinical trials [2]. Therefore, there is an urgent need to explore new therapeutic approaches. Traditional Chinese Medicine (TCM) has shown potential and unique advantages in the prevention and treatment of pulmonary fibrosis [3]. Its multi-component, multi-target mechanism may compensate for the limitations of single-target Western drugs. This article will focus on the research progress of pulmonary fibrosis mouse models from 2015 to 2025, integrating TCM theory and modern mechanisms, to review the pathogenesis, model types, signaling pathways, and the latest research advances in TCM intervention.

2. Overview of Pulmonary Fibrosis Mouse Models

Various mouse models are employed to simulate key characteristics of human pulmonary fibrosis. Each model differs in induction methods, advantages, and limitations. While no single model can fully replicate human idiopathic disease, the integrated use of different models helps provide comprehensive insights. Below is an overview of commonly used and emerging mouse models of pulmonary fibrosis:

Bleomycin-induced model: A classic chemical injury model, typically induced by a single intratracheal instillation of bleomycin (BLM) solution, causing acute alveolar injury that develops into fibrosis within 1–3 weeks [4]. Intratracheal administration is the most widely used protocol, producing patchy fibrotic lesions, with histology revealing significant collagen deposition under Masson staining and alveolar structure destruction [5]. The model's advantages include simple establishment and a well-defined fibrotic phenotype, making it the "gold standard" preclinical model for antifibrotic drug testing. Its main drawbacks are the acute and reversible disease course—partial fibrosis regression may occur around 4 weeks post-administration due to epithelial repair—which does not align with the persistent progression of human IPF. Additionally, BLM induces intense early inflammatory responses, incompletely reflecting the insidious, chronic injury process in IPF [6]. To better mimic chronic fibrosis, delayed intervention (after the acute inflammatory peak) or repeated low-dose administration can prolong fibrotic persistence [7].

Silica (crystalline silica dust)-induced model: Induced by inhalation or intratracheal instillation of crystalline silica particles, simulating occupational dust exposure-related fibrosis such as silicosis [8]. The lesions exhibit more pronounced chronic progressive features: long-term particle retention in the lungs triggers macrophage-mediated

persistent inflammation and granuloma-like fibrotic nodules. Histologically, collagen deposition often forms clusters, with silicotic-like small granulomas appearing, and fibrosis tends to be relatively focal and nodular. Compared to the BLM model, silica dust-induced fibrosis progresses more slowly and persistently, with early inflammation dominated by macrophages and accompanied by inflammasome (e.g., NLRP3) activation [9]. This model is suitable for studying fibrosis under long-term repetitive injury scenarios and screening chronic antifibrotic drugs. A limitation is its emphasis on inflammatory/granuloma pathways, differing from idiopathic IPF's unknown etiology [10]; however, as a "persistent exogenous stimulation" paradigm, it complements the acute BLM model.

Genetically engineered and spontaneous models: These involve chronic induction of fibrotic phenotypes in mice through genetic manipulation. One type is the transgenic overexpression model, typically exemplified by specific induction of TGF-β1 overexpression in alveolar epithelium, which can lead to progressive interstitial fibrosis, directly demonstrating the central role of TGF-β signaling in fibrosis [11]. Another type is the pathogenic knock-in model, where human familial IPF-associated mutant genes (such as SFTPC-I73T, SFTPA2 mutations, etc.) are introduced into mice, triggering spontaneous fibrosis with aging. The mechanism involves protein folding stress and chronic damage in alveolar epithelial type II cells [12]. There are also conditional gene knockout models, such as specific deletion of key genes (Sin3a, Slc39a8, etc.) in AEC2 cells, which can induce spontaneous progressive fibrosis, highlighting the central role of alveolar epithelial homeostasis dysregulation in fibrosis [13]. Additionally, aged mice themselves (>18 months old) are more susceptible to lung injury and can serve as aging-related models. Overlaying low-dose BLM or chronic infection ("second hit") on aged mice can better simulate the fibrotic susceptibility of the elderly population [14]. The limitations of genetic and spontaneous models lie in their ability to often only replicate certain aspects of the disease (e.g., abnormalities in a specific signaling pathway), variability in penetrance and severity, long establishment cycles, and the need for additional triggers in some cases to manifest phenotypes. Nevertheless, these models hold significant value in mechanistic studies and potential target validation.

Other emerging models: These include radiation injury models (where pulmonary fibrosis develops months after chest irradiation, with a slow progression, simulating clinical radiation pneumonitis/fibrosis) [15]; particulate/toxin models (inhaling asbestos fibers, PM2.5 particles, or administering alkaloids like sanguinarine, paraquat, or long-term high-dose amiodarone, which can induce corresponding fibrosis, simulating lung injury caused by environmental toxins or drugs) [16]; infection and superimposed models (chronic infection with gamma herpesvirus or high-titer adenoviral vectors in aged mice can induce or worsen fibrosis, and superimposing initial injuries like BLM or enzyme-inducing agents such as FITC with respiratory viral infections can simulate acute exacerbations of fibrosis) [17]; humanized/chimeric models (transplanting human lung fibroblasts or fibrotic tissue fragments into immunodeficient mouse lungs to construct in vivo models with partial human cell behavior); and in vitro novel technology platforms (ex vivo lung tissue slices, lung "organ-on-a-chip," lung organoids, etc., which can be used for drug screening and mechanism validation) [18].

Summary: Overall, chemical injury and particulate exposure models emphasize exogenous lung injury, while genetic engineering models highlight intrinsic susceptibility factors in the organism. Combining the two can more comprehensively reproduce the complex pathogenesis of IPF. Future research tends toward multi-model validation: for example, rapid efficacy screening in BLM models, followed by validation in chronic or genetic models, supplemented by evidence from humanized cells and tissue samples to enhance the reliability and translational value of findings.

3. Pathological Mechanisms in Mouse Models

Research on mouse models of pulmonary fibrosis has revealed numerous pathological processes involved in the development and progression of fibrosis, including impaired epithelial injury repair, immune-inflammatory imbalance, abnormal fibroblast activation, intercellular signaling networks, and cellular plasticity changes. The main mechanistic highlights are as follows:

3.1 Alveolar Epithelial Cell Injury and Impaired Repair

Repeated injury to type II alveolar epithelial cells (AEC2) is considered one of the initiating events of fibrosis. Persistent epithelial damage leads to dysregulated repair processes, with many epithelial cells undergoing trans differentiation into mesenchymal phenotypes (EMT) and releasing profibrotic mediators. Continuous expression of TGF-β1 in transgenic mice can induce progressive scar formation, directly linking chronic epithelial injury to the fibrotic process [19]. Since large areas of alveolar epithelial denudation and exposed basement membranes are commonly observed in the lung tissues of IPF patients, this "epithelial-mesenchymal imbalance" is regarded as the key pathological basis for fibrosis initiation.

3.2 Fibroblast Activation and Myofibroblast Accumulation

Hyperactivated fibroblasts and their differentiated myofibroblasts (α-SMA positive) proliferate excessively and deposit excessive extracellular matrix (ECM), representing the core manifestation of fibrosis [20]. TGF-β is widely recognized as the central signaling pathway for fibroblast activation, with additional pathways such as PDGF, Wnt/β-catenin, Hedgehog, and integrins collectively driving myofibroblast accumulation and collagen production. Consequently, elevated levels of TGF-β1, collagen I, and α-SMA are often detected in models. Large numbers of activated myofibroblasts form so-called "fibroblastic foci," which are considered markers of irreversible progressive fibrotic changes.

3.3 Immune-inflammatory Mediation

In the early stages of fibrosis, model animals often exhibit significant inflammatory cell infiltration in the lungs,

including neutrophils, macrophages, and lymphocytes [21]. Macrophage polarization toward the M2 phenotype (pro-repair type) is particularly prominent during fibrosis progression, with M2-like macrophages secreting profibrotic factors such as TGF-β, IL-13, and CCL18, stimulating fibroblast activation. However, some models show sustained fibrotic progression without significant inflammatory responses, suggesting the existence of sterile chronic wound-healing pathways. In other words, fibrosis can be driven without obvious inflammation, which aligns with the lack of acute inflammatory symptoms commonly seen in IPF patients. Therefore, interventions targeting immune inflammation must be timed carefully: overly early or strong suppression may impair tissue repair, while delayed intervention may prove ineffective.

3.4 Cytokine and Growth Factor Network

In fibrotic lung tissue, altered levels of multiple cytokines and growth factors form a complex network. In addition to the widely upregulated TGF-β1, Th2-associated factors such as IL-13, chemokines like CCL2/CCR2, and fibroblast growth factors such as CTGF are also elevated [22]. Angiogenic factors exhibit complex biphasic effects (with reports of both pro-fibrotic and protective roles). This suggests that fibrosis is not driven by a single factor but rather by dysregulation of multiple signals, making multi-target combination therapy a potential future direction for intervention.

3.5 ECM Remodeling and Mechanobiology

Excessive deposition and remodeling of the extracellular matrix (ECM) during pulmonary fibrosis are among the primary causes of irreversible pathology. Overaccumulation of collagen and other ECM components, coupled with an imbalance between matrix metalloproteinases (MMPs) and their inhibitors (TIMPs) as well as lysyl oxidase (LOX)-mediated collagen cross-linking, leads to progressive tissue stiffening and stabilization [23]. The increased tissue stiffness itself further stimulates fibrosis: thickened and rigid ECM mechanically activates latent TGF-β via integrin receptors (e.g., αvβ6), perpetuating TGF-β activation and creating a biomechanical-biochemical positive feedback loop. Thus, fibrosis is a dynamic process involving mechanobiological changes, and targeting inflammation or fibroblasts alone without addressing matrix stiffness may limit therapeutic efficacy.

3.6 Cellular Plasticity and Senescence

Single-cell sequencing technologies have revealed lineage reprogramming in pulmonary fibrosis. For example, abnormal KRT5-/KRT17+ basal-like epithelial cell populations have been identified in human IPF lungs, representing cells attempting but failing to mature after repeated injury [24]. Correspondingly, Krt8+ transitional epithelial cells have been detected in bleomycin (BLM)-induced mouse lungs, likely representing an intermediate state during regeneration. In contrast, human IPF lesions exhibit epithelial regeneration arrest, whereas mouse models tend to complete regeneration with partial fibrosis reversal. Additionally, multiple cell types (epithelial, endothelial, mesenchymal) in fibrotic tissue display premature senescence, overexpressing cell cycle inhibitors such as p16Ink4a and p21. The senescence-associated secretory phenotype (SASP) secreted by senescent cells promotes chronic inflammation and fibrotic deposition. Treating model mice with senolytic drugs (e.g., dasatinib + quercetin) reduces senescent cell burden and attenuates fibrosis, suggesting that cellular senescence is both a key contributor to fibrosis and a potential therapeutic target.

3.7 Summary

In conclusion, the common pathogenesis of pulmonary fibrosis follows the sequence "repeated epithelial injury → sterile inflammatory repair response → fibroblast / myofibroblast activation and proliferation → progressive ECM stiffening." Age-related factors, cellular plasticity changes, and altered mechanical environments further modulate fibrosis progression. These insights provide a theoretical foundation for multi-pathway intervention in pulmonary fibrosis.

4. Correspondence Between TCM Theory and the Pathogenesis of Pulmonary Fibrosis

Traditional Chinese Medicine (TCM) offers unique interpretations of the pathogenesis and progression of pulmonary fibrosis, forming several theoretical frameworks. These TCM concepts of pathogenesis exhibit a certain degree of correspondence with modern medical understanding:

"Qi Deficiency and Phlegm Stagnation": Refers to a pathological state characterized by deficiency of vital qi, impaired qi movement, and internal accumulation of damp-turbidity and stasis. Patients with pulmonary fibrosis often exhibit systemic metabolic dysfunction and waste accumulation, while cellular-level observations reveal mitochondrial dysfunction and impaired autophagy, which align with the TCM states of "qi deficiency" and "phlegm stagnation" [25]. Studies have shown that decreased ATP production capacity and accumulation of damaged mitochondria in the lung tissues of IPF patients correlate with TCM's "qi deficiency" and "phlegm-stasis" states. TCM herbs that tonify lung and kidney qi (e.g., ginsenoside Rg1, icariin) have been shown to promote mitochondrial autophagy, restore cellular energy metabolism, and enhance the body's anti-fibrotic capacity.

"Dryness Damaging Lung Collaterals": Refers to a pathogenic mechanism where dryness pathogens or yin deficiency - induced internal dryness injure the lung collaterals, depleting body fluids and leading to desiccation of lung tissue and impaired blood circulation. One histological feature of pulmonary fibrosis is alveolar epithelial cell detachment, exposed basement membranes, "dry" interstitial tissue, and sparse capillaries—consistent with the TCM concept of "lung collaterals damaged by dryness-heat." This theory posits that consumption of yin fluids deprives the lungs of moisture, causing collateral vessel stasis and triggering fibrosis. Treatment should thus focus on nourishing yin, moistening the lungs, and activating collaterals. For example, yin-nourishing herbs like Ophiopogon japonicus and Glehnia littoralis have been shown in animal models to reduce lung inflammation and collagen deposition, serving as effective interventions to moisten dryness and protect lung collaterals

[26]. Some scholars propose that the prevention and treatment of pulmonary fibrosis should adhere to the principle of "preventing dryness and safeguarding collaterals."

"Internal Binding of Stasis and Toxin": In traditional Chinese medicine (TCM), "stasis" refers to impeded blood circulation, while "toxin" denotes residual pathological products in the body (such as inflammatory pathogenic factors). Their internal binding in the lungs can be understood as persistent microcirculatory disturbances and the formation of inflammatory fibrotic foci. Modern research has found that pulmonary fibrotic lesions are often surrounded by microthrombi and extensive neutrophil extracellular traps (NETs) deposits. These NETs can adhere to extracellular DNA and proteases, causing secondary tissue damage, corresponding to the TCM states of "blood stasis obstructing collaterals" and "toxic pathogens scorching the lungs." Reports indicate that NETs levels correlate with the severity of pulmonary fibrosis and can exacerbate capillary obstruction and matrix destruction [27]. Targeting this mechanism, TCM can resolve the binding of stasis and toxin through blood-activating and stasis-resolving, heat-clearing, and detoxifying treatments. For example, blood-activating herbs like Salvia miltiorrhiza (Danshen) and Carthamus tinctorius (Honghua) can improve pulmonary microcirculation and reduce collagen deposition, while heat-clearing and bowel-purging herbs like Rheum palmatum (Dahuang) can inhibit excessive neutrophil activation and reduce NETs formation.

"Dysfunction of Opening, Closing, and Pivoting": Derived from TCM's Sanjiao (triple energizer) theory, this refers to the disorder of the body's opening, closing, and regulatory functions. Some attribute the pathogenesis of idiopathic pulmonary fibrosis (IPF) to abnormal dispersal (opening) of the upper energizer (lungs), impaired transportation and pivoting of the middle energizer (spleen), and insufficient qi reception (closing) of the lower energizer (kidneys) [28]. Failure of the lungs to open leads to internal accumulation of phlegm turbidity; failure of the spleen to transport results in endogenous dampness turbidity; and failure of the kidneys to receive qi disrupts the ascending-descending qi mechanism. Collectively, Sanjiao dysfunction causes fluid metabolism disorders and accumulation of phlegm, stasis, and toxin in the lungs. Treatment should therefore integrate lung-dispersing, spleen-strengthening, and kidney-tonifying methods to regulate the opening, closing, and pivoting functions, restoring the body's overall balance. This theory emphasizes that pulmonary fibrosis is not merely a localized lung issue but involves systemic metabolic imbalances, requiring holistic TCM-guided comprehensive treatment.

"Preserving Sweetness to Restore Fluids": This is a recently proposed concept guiding the treatment of radiation-induced pulmonary fibrosis [29]. Radiation injury depletes lung yin fluids, leading to early-stage lung dryness, scorching, and blood stasis nodules. "Preserving Sweetness to Restore Fluids" advocates the early use of sweet-moistening and nourishing agents (mild yin-nourishing herbs with sweet properties) to protect residual fluids and mitigate radiation-induced lung yin depletion. In the middle and late stages, blood-activating and detoxifying herbs are added to disperse the binding of stasis and toxin. Animal studies support this approach, showing that yin-nourishing herbs like Adenophora stricta (Shashen) and Ophiopogon japonicus (Maidong) can reduce pulmonary fibrosis in irradiated mice. This theory provides a framework for stage-specific treatment of radiation-induced pulmonary fibrosis: early-stage yin nourishment to prevent dryness and middle-to-late-stage blood activation and stasis resolution to improve prognosis.

5. Therapeutic Intervention Strategies and Research Findings

Advances in Modern Drugs and Intervention Strategies: In mouse models, numerous modern drugs and emerging therapies have been employed for pulmonary fibrosis intervention research, which can be broadly categorized into the following types:

Standard antifibrotic drugs: Pirfenidone and nintedanib are currently the standard clinical antifibrotic medications. Mouse experiments demonstrate that both can reduce lung tissue collagen deposition and fibrosis scores, but clinically they can only slow the decline in pulmonary function without reversing established fibrosis [30]. This has driven the exploration of more potent drugs or combination therapies. For example, some studies have attempted to combine other drugs with nintedanib to achieve synergistic antifibrotic effects.

Targeting the growth factor pathway: Since TGF-β is a central contributor to fibrosis, interventions targeting TGF-β and its downstream pathways have become a research focus, including neutralizing TGF-β1 antibodies, TGF-β receptor kinase inhibitors, and Smad protein blockers. In mouse models, these approaches have often been shown to reduce fibrosis severity [31]. However, since TGF-β signaling is also crucial for normal tissue homeostasis, the safety and efficacy of such therapies present challenges. In fact, systemic applications of multi-target tyrosine kinase inhibitors like imatinib (targeting PDGF and others) failed to meet primary endpoints in clinical trials. This has prompted researchers to seek more precise novel targets, such as recently reported TNIK inhibitors and ROCK2 inhibitors, which have demonstrated anti-fibrotic potential in models [32].

Anti-inflammatory and Immune Regulation: Broad-spectrum anti-inflammatory approaches alone are typically insufficient to reverse established fibrotic lesions. Some studies have focused on specific inflammatory pathways, such as blocking the CCR2/CCL2 chemokine axis or inhibiting M2 macrophage polarization, which have shown positive results in certain models but overall clinical translation has been unsuccessful [33]. Current understanding suggests that inflammation is a key driver in the early stages of fibrosis, but once fibrosis enters the chronic progression phase, anti-inflammatory interventions alone are unlikely to reverse the condition. Therefore, combined interventions targeting both inflammation and fibrosis are now emphasized.

Antioxidant and Epithelial Protection: The antioxidant N-acetylcysteine (NAC) was once highly anticipated, but clinical results have been inconclusive. Research has found that reducing alveolar epithelial cell apoptosis benefits fibrosis alleviation, suggesting that protecting epithelial cells may be a viable approach [34]. For instance, certain

antioxidant small molecules or mitochondrial-targeting agents have shown effects in reducing epithelial damage and mitigating fibrosis in models, though they remain distant from clinical application.

Matrix Remodeling and Anti-fibrotic Microenvironment: Focusing on the excessively stable ECM in fibrotic tissues, some studies have used LOXL2 enzyme inhibitors to reduce collagen cross-linking or administered matrix metalloproteinases to accelerate collagen degradation. Such interventions can promote lesion regression when applied in the early to mid-stages of fibrosis, but clinical validation remains insufficient [35]. Timing is crucial: premature use of strong proteases may damage normal matrix, while delayed intervention may find fibrotic tissue already resistant to degradation.

Cell Therapy and Exosomes: Adult stem cell transplantation (e.g., bone marrow mesenchymal stem cells, MSCs) has shown some efficacy in pulmonary fibrosis models, possibly through paracrine anti-inflammatory and anti-fibrotic effects, but their limited retention and survival time in recipient lungs lead to inconsistent results [36]. In contrast, exosomes derived from stem cells or lung progenitor cells, serving as carriers of cytokines, have been proven effective when delivered via nebulized inhalation, promoting alveolar epithelial regeneration and reducing fibrosis [37]. Additionally, transplanting induced pluripotent stem cell (iPSC)-derived alveolar epithelial cells into fibrosis models can partially reconstruct the epithelial barrier, demonstrating the potential of regenerative therapy [38].

Senolytic Therapy: In response to the accumulation of cellular senescence in fibrotic tissues, recent years have proposed the strategy of using senolytic agents. The combination of dasatinib and quercetin (D+Q) selectively clears p16Ink4a-positive senescent cells in aged BLM mice, reduces pro-inflammatory SASP factors, improves lung function, and alleviates fibrosis [39]. This achievement has led to small-scale clinical trials exploring the safety and feasibility of senolytics in IPF patients.

Combination and Sequential Therapy: Given that pulmonary fibrosis involves multiple pathological processes, single-drug therapies often prove ineffective. Animal studies show that multi-pathway drug combinations and appropriately timed administration based on disease stage can significantly enhance efficacy. For example, early-stage anti-inflammatory and antioxidant drugs control inflammatory damage, while mid-to-late-stage anti-fibrotic and tissue-remodeling drugs achieve better lung function improvement than single regimens through two-phase relay therapy [40]. However, combination therapy requires balancing systemic toxicity and patient compliance, and the search for optimal combinations and dosages remains ongoing.

Summary: Given the limitations of single models, it is recommended that new drug candidates be validated for efficacy in at least two different types of fibrosis models, supplemented by mechanistic studies using human pulmonary fibrosis cells or clinical samples to improve the probability of successful clinical translation.

6. Discussion and Outlook

In summary, recent research on pulmonary fibrosis mouse models has significantly enriched our understanding of this disease and provided an important platform for drug development. The integration of traditional Chinese medicine (TCM) research has brought new perspectives and approaches to this field. Modern studies are accelerating the convergence of traditional empirical knowledge with scientific experimentation. TCM has demonstrated multi-faceted advantages in the prevention and treatment of pulmonary fibrosis: it not only improves the internal environment of patients through holistic regulation such as replenishing qi, nourishing yin, and activating blood circulation to remove stasis, but also simultaneously targets multiple fibrotic pathways at the molecular level to achieve anti-inflammatory, anti-fibrotic, and tissue-repairing effects. Furthermore, modern detection technologies provide robust support for elucidating the mechanisms of TCM action and make therapeutic efficacy evaluation more objective and intuitive. These developments have established a foundation for the objective assessment of TCM's therapeutic effects. With deepening mechanistic research and the accumulation of high-quality clinical evidence, practical treatment strategies for refractory pulmonary fibrosis are expected to emerge, bringing new hope to patients.

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