

Mechanisms and Efficacy of Mesenchymal Stromal Cells in Progressive Pulmonary Fibrosis

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ABSTRACT

Progressive pulmonary fibrosis (PPF) is a clinical phenotype characterized by worsening fibrosis, declining lung function, and progressive respiratory symptoms despite appropriate treatment of the underlying interstitial lung disease (ILD). It may develop in several fibrotic ILDs other than idiopathic pulmonary fibrosis, including fibrotic hypersensitivity pneumonitis, nonspecific interstitial pneumonia, and connective tissue disease-associated ILD. PPF is associated with irreversible structural lung damage, reduced quality of life, and increased mortality. Despite the development of standard antifibrotic agents, specifically nintedanib and pirfenidone, therapeutic failure and disease progression remain common outcomes. Consequently, mesenchymal stromal cells (MSCs) represent a promising therapeutic approach due to their immunomodulatory, anti-inflammatory, and antifibrotic properties. This review evaluates the rationale for MSC-based therapy in fibrotic lung disease, summarizes available preclinical and clinical evidence, and discusses the limitations, safety considerations, and research priorities that must be addressed before clinical application can be established.

Keywords: mesenchymal stem cells, interstitial lung disease, progressive pulmonary fibrosis, regenerative medicine, antifibrotic therapy.

Introduction

Interstitial lung diseases (ILD) remain one of the most challenging entities in respiratory medicine, characterized by progressive parenchymal fibrosis that induces severe gas-exchange impairment, chronic respiratory insufficiency, and high mortality [1]. Epidemiologically, idiopathic pulmonary fibrosis (IPF) shows distinct geographic variability, with higher incidence in North America and Europe (3-9 cases per 100,000 person-years) compared to South America and East Asia (< 4 cases per 100,000 person-years) [1].

A primary impediment to clinical recovery is the inherently restricted regenerative capacity of native pulmonary architecture compared to the robust cellular turnover seen in other somatic organ systems. Among these, fibrotic hypersensitivity pneumonitis (HP), non-specific interstitial pneumonia (NSIP), IPF, and systemic

sclerosis-associated interstitial lung disease (SSc-ILD) frequently exhibit a progressive pulmonary fibrosis (PPF) phenotype. This clinical course is characterized by an unremitting decline in pulmonary function and a refractory response to conventional therapeutic interventions.

According to official ATS/ERS/JRS/ALAT guidelines, PPF is defined as a progressive disease phenotype occurring in a patient with a known or unknown fibrotic ILD other than IPF [2, 3]. To meet the formal diagnostic criteria, the patient must present with at least two of the following three parameters within a 12-month period without an alternative clinical clarification: unexplained worsening of respiratory symptoms, an absolute drop in forced vital capacity (FVC decline $\geq$ 5%), diffused capacity of the lung for carbon monoxide decrease (DLCO $\geq$ 10%), evidence of advancing fibrosis (expanding traction bronchiectasis, new reticulation, ground-glass opacity, or honeycombing by HRCT).

Current anti-fibrotic therapies, including pirfenidone and nintedanib, merely slow functional decline without reversing fibrosis [4]. Nintedanib, a tyrosine kinase inhibitor, demonstrated the ability to reduce the annual decline of FVC by approximately 107 mL compared to placebo [4]. Many patients continue to experience disease progression and drug-related adverse events such as diarrhea, hepatic enzyme elevation, and increased bleeding risk [4]. Lung transplantation remains the only definitive treatment but is limited by donor availability, cost, and perioperative risks. Long-term oxygen therapy provides symptomatic relief but does not modify disease progression [5]. Hence, there is a critical need for novel, safe, and effective therapies capable of altering the natural course of fibrotic ILDs.

Developing more efficient therapies for pulmonary fibrosis remains a difficult task, as the prevalence of this condition continues to rise worldwide, leading to a substantial increase in mortality, morbidity, and burden of healthcare system. Consequently, the urgent development of novel, safe, efficacious, and highly bioavailable therapeutic strategies remains imperative.

Mesenchymal stromal cells (MSCs) isolated from bone marrow (BM), umbilical cord blood (UCB), and adipose tissue (AT) remain at the forefront of regenerative medicine and advanced therapeutics [6, 7]. This article provides an overview of preclinical and clinical trial data evaluating MSC transplantation for the management of ILD presenting with PPF phenotype. Additionally, it analyzes critical procedural variables essential for optimizing therapeutic protocols. Specifically, it examines alternative cell sources, delivery routes, administration timing, dosing thresholds, and ex vivo preconditioning strategies. The article suggests an optimized approach for guiding the development of subsequent clinical trials aimed at finding effective treatments for this complex disease.

Pathogenesis of Pulmonary Fibrosis

The biomolecular cascade underlying PPF is driven by interconnected cellular and molecular mechanisms that contribute to progressive lung remodeling and irreversible fibrosis (Figure 1).

The cellular progression of pulmonary fibrosis is closely associated with dysregulated repair mechanisms in the alveolar epithelium. Persistent inflammatory signaling and prolonged activation of alveolar epithelial cells trigger pathological communication with interstitial lung cells. This process promotes interstitial cell recruitment and excessive extracellular matrix production, resulting in alveolar wall thickening and reduced lung compliance. The ongoing buildup of myofibroblasts and matrix proteins amplifies mechanical stress in fibrotic areas, creating a self-sustaining cycle of tissue remodeling that progressively impairs lung structure and function [8].

Cellular homeostatic imbalance is central to this cascade. Impaired autophagy induces epithelial-mesenchymal transition (EMT) in alveolar epithelial cells and contributes to fibrosis by disrupting epithelial-fibroblast communication [9], while promoting reactive oxygen species (ROS) overproduction and oxidative injury [10]. Excessive generation of ROS promotes epithelial injury and activates NF- κ B signaling, resulting in increased MUC5B expression. MUC5B overproduction impairs mucociliary clearance and contributes to persistent epithelial dysfunction, thereby facilitating fibrotic remodeling of the lung [11]. The pathogenesis of IPF is a multifaceted process, and its progression is often unpredictable. In IPF, mutations in genes responsible for maintaining lung epithelial integrity, such as ABCA3, SFTPC, and SFTPA2, as well as aberrant expression of MUC5B, contribute to dysfunction of the pulmonary epithelial mucosal barrier [12].

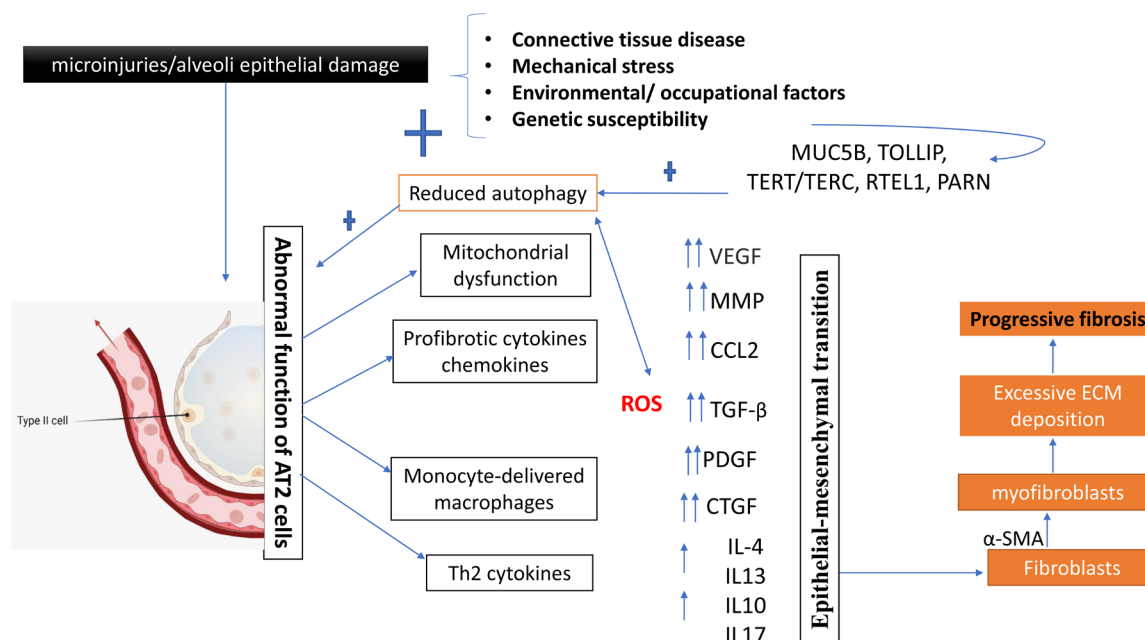


Figure 1 – Key mechanisms driving pulmonary fibrosis progression. PPF pathogenesis includes repetitive alveolar epithelial cell injury, activation of profibrotic signaling pathways, fibroblast proliferation and differentiation into myofibroblasts, epithelial-mesenchymal transition (EMT), dysregulated autophagy, and impaired mitochondrial quality control (“+” - stimulation; “↑” - increased secretion; “↑↑” - markedly increased secretion; “→” - direction of signaling or disease progression). ROS - Reactive oxygen species, AT2 cells - alveolar epithelial type II cells, α -SMA - alpha-smooth muscle actin, MUC5B - Mucin 5B, TOLLIP - Toll-interacting protein, TERT - Telomerase reverse transcriptase, TERC - Telomerase RNA component, RTEL1 - Regulator of telomere elongation helicase 1, PARN - Poly(A)-specific ribonuclease, ECM - Extracellular matrix, MMP - Matrix metalloproteinases, CCL2 - C-C motif chemokine ligand 2, TGF- β - Transforming growth factor beta, PDGF - Platelet-derived growth factor, IL — Interleukin).

Genetic determinants significantly influence host susceptibility to the disease, encompassing specific single nucleotide polymorphisms (SNPs) and pathogenic mutations that compromise epithelial integrity. These genetic variations are strongly associated with the impairment of telomere length maintenance - a homeostatic pathway strictly regulated by a core cluster of proteins, including telomerase reverse transcriptase, telomerase RNA component, poly(A)-specific ribonuclease, and regulator of telomere elongation helicase [13].

Additionally, alterations in Toll-interacting protein (TOLLIP), a negative controller of the transforming growth factor- β (TGF- β) signaling cascade and a vital regulator of innate immune responses mediated by Toll-like receptors, have been linked to reduced TLR mRNA levels and increased vulnerability to respiratory infections [13]. Through genome-wide association studies, it has been discovered that a specific genetic variation (rs35705950) situated in the regulatory region of the MUC5B gene is strongly linked to a higher likelihood of developing IPF [14]. MUC5B is involved in airway mucus production and lung innate immunity. Its overexpression is associated with impaired mucociliary clearance and increased severity of fibrosis. The minor allele rs35705950 enhances the expression of MUC5B in the epithelial cells of small airways, and DNA methylation also plays a role in genetic predisposition. Mechanistically, the mucus ERN2-XBP1S (Endoplasmic Reticulum to Nucleus signaling 2- X-box Binding Protein 1, spliced form) pathway upregulates MUC5B expression via an unfolded protein response-dependent mechanism linked to this variant [15-17].

Molecular signaling pathways further amplify the fibrotic response. Numerous studies have demonstrated that interleukin-1 β (IL-1 β) stimulates the release of TGF- β , a key player in the process of fibrogenesis in lung cells. In particular, the TGF- β /SMAD pathway is associated with the progression of pulmonary fibrosis [18].

In mice treated with bleomycin, the expression of LRRK2 in alveolar type II epithelial cells (AT2) is significantly reduced. This reduction leads to severe dysfunction of these cells, characterized by impaired autophagy and accelerated cellular aging. Moreover, LRRK2-deficient AT2 cells have a greater ability to attract profibrotic macrophages through the CCL2/CCR2 signaling pathway, resulting in enhanced macrophage-mediated profibrotic responses. Taken together, these findings suggest that LRRK2 is essential for preventing AT2 cell dysfunction and regulating innate immune responses to prevent pulmonary fibrosis [19].

In response to tissue injury, inflammatory cells infiltrate the damaged region and secrete cytokine precursors, including pro-IL-1 β and pro-IL-18, as well as type I interferons. These factors activate TLR2- and TLR4-mediated signaling pathways, resulting in NLRP3 inflammasome assembly and caspase-1 activation. Consequently, IL-1 β and IL-18 are processed into their biologically active forms, promoting pyroptotic cell death and amplifying the inflammatory response [20]. As a result, profibrotic mediators such as TGF- β 1, PDGF, CCL2, and CXCL12 are produced which contribute to the progression of fibrosis [21, 22].

While animal models of pulmonary fibrosis cannot fully recapitulate the pathological features of IPF, they have substantially advanced our understanding of the mechanisms underlying fibrogenesis. Studies using these models have identified multiple profibrotic pathways, including those mediated by TGF- β , CTGF, FGF2, PDGF, microRNAs, impaired autophagy, developmental signaling cascades, lysophosphatidic acid (LPA), matrix metalloproteinase 7 (MMP-7), and lysyl

oxidase-like 2 (LOXL2) [23]. Among these mediators, TGF- β 1 is considered a central driver of fibrosis. It induces epithelial cell apoptosis, promotes EMT, and stimulates the expression of additional profibrotic factors, including vascular endothelial growth factor (VEGF) and connective tissue growth factor (CTGF). Together, these mediators establish a positive feedback mechanism that sustains and amplifies fibrotic signaling [24].

Cellular abnormalities such as telomere shortening, oxidative stress, mitochondrial dysfunction, and impaired proteostasis associated with endoplasmic reticulum stress collectively limit the regenerative capacity of alveolar epithelial cells. This dysfunctional state favors the release of profibrotic mediators that activate fibroblasts and drive their differentiation into myofibroblasts [1, 25, 26]. Myofibroblasts are distinguished by the expression of α -smooth muscle actin (α -SMA) and fibroblast activation protein (FAP). Compared with fibroblasts, they produce significantly larger amounts of extracellular matrix (ECM), making them the principal effector cells responsible for collagen deposition and fibrotic remodeling in the lung [27].

Rationale for the Use of Mesenchymal Stromal Cells

MSCs represent a compelling therapeutic candidate for progressive pulmonary fibrosis, a status sustained by their minimal baseline immunogenicity, straightforward isolation protocols, anti-inflammatory capabilities, and extensive ex vivo proliferation capacity. A defining hallmark of MSCs is their robust secretome, rich in bioactive factors that promote tissue remodeling, including angiogenesis and immunomodulation. These collective biological properties together with their ease of culture expansion, have established MSCs as a preeminent cell type under investigation within regenerative medicine [28].

MSCs present a compelling cell-based therapeutic platform due to their intrinsic ability to migrate to sites of injury ("homing" effect) [29]. This directional migration is orchestrated via chemotaxis, wherein a localized chemokine gradient synthesized and released by the damaged pulmonary microenvironment attracts and guides the exogenously delivered cells to the target niche [30, 31]. Moreover, following the most prevalent delivery route utilized in clinical protocols - intravenous injection - quantitative imaging revealed that over 80% of MSCs accumulate within the lung vasculature within minutes of infusion, before subsequently redistributing to the liver and spleen [32].

Emerging evidence indicates that MSCs derived from different sources vary in their proliferative ability, differentiation potential, and secretory profiles due to microenvironmental imprinting and niche-dependent properties [33, 34]. This variability may influence their therapeutic efficacy in PPF and should be considered carefully when selecting an appropriate cell source.

The therapeutic impact of MSCs is mediated through both direct cytokine secretion and the release of extracellular vesicles (EVs). Importantly, the MSC secretome adapts dynamically to the inflammatory microenvironment: while they can produce homeostatic and anti-inflammatory mediators (such as IL-10, prostaglandin E2 (PGE2), and TNF-stimulated gene-6), MSC may also secrete specific pro-inflammatory cytokines, specifically IL-1 β , IL-6, and IL-8, under certain priming conditions [35].

In the context of fibrotic remodeling, MSCs effectively inhibit fibroblast activation via suppression of the TGF- β signaling pathway [36]. TGF- β 1 efficiently upregulates invasive molecular signatures characteristic of fibrotic tissue phenotypes,

while concurrently driving the differentiation of quiescent normal fibroblasts into active myofibroblasts. Notably, co-culture or treatment with MSCs facilitates a reversible de-differentiation of myofibroblasts into a distinct subpopulation of fibroblast-like cells. This phenotypic reversion is mediated via the selective suppression of the canonical TGF- β -SMAD2/3 signaling axis. Crucially, these derived fibroblast-like cells exhibit enhanced proliferative capacity yet retain functional responsiveness to exogenous TGF- β 1, rendering them susceptible to subsequent re-induction toward the myofibroblasts lineage [36]. Furthermore, in vivo models demonstrate that the MSC secretome actively reduces the accumulation of ECM proteins. For instance, An et al. identified 32 proteins within the umbilical cord-derived MSC (UC-MSC) secretome capable of suppressing the expression of pro-fibrotic mediators, including specific metalloproteinases, collagens, and Smad proteins. Concurrently, MSC-derived factors like milk fat globule-EGF factor 8 (MFGE8) suppress transforming growth factor- β type I receptor (TGF β R1) expression, exerting potent anti-fibrotic effects [37].

Beyond direct anti-fibrotic activity, MSCs stimulate tissue repair through potent angiogenic and paracrine signaling. Under optimal culture conditions, MSCs secrete key angiogenic factors, specifically VEGF-A, angiopoietins, IGF-1, and hepatocyte growth factor (HGF), which prompt endothelial cell sprouting, thereby restoring microvascular networks and oxygenation to regenerating tissues [38, 39].

MSC can differentiate into different cell lineages, including functional pulmonary epithelial and endothelial cells [6]. Importantly, rather than differentiating directly into new epithelial or endothelial lineages in large numbers, MSCs primarily drive structural regeneration by stimulating the tissue's resident progenitor cells via robust paracrine signaling. Through the secretion of paracrine mediators like keratinocyte growth factor (KGF) and HGF, MSCs trigger nearby epithelial cells to proliferate, migrate, and close barrier defects [6].

Preclinical Studies of Mesenchymal Stem Cells in PPF

Evaluations across animal models of pulmonary fibrosis demonstrate that MSC administration attenuates collagen deposition, decreases alveolar wall thickening, and improves survival. MSCs secrete angiogenic and anti-inflammatory factors such as VEGF, IL-10, and HGF, which contribute to restoration of alveolar architecture and microvascular integrity.

The pooled preclinical data indicated that MSCs exert a potent protective effect, significantly enhancing 14-day survival and down-regulating inflammatory drivers such as bronchoalveolar neutrophil infiltration and TGF- β expression. Structurally, MSCs consistently mitigated collagen accumulation and improved Ashcroft fibrosis scores [40].

Preclinical data robustly support the safety and efficacy of MSC for PPF [41]. MSC treatment markedly boosted survival rates and mitigated fibrosis in animal models [42]. A fixed-effects meta-analysis of 12 preclinical studies demonstrated low heterogeneity ($I^2 = 0\%$ and $p = 0.84$) and a survival benefit for MSC therapy. Specifically, animals receiving MSCs exhibited a significantly higher survival rate than untreated controls (OR 3.10, 95% CI 2.06–4.67, $p < 0.001$) [42].

MSC transplantation significantly reduced the Ashcroft fibrosis score [43, 44]. Studies demonstrated a significant reduction in cell infiltration in bronchoalveolar lavage fluid mediated by MSC intervention [43–45]. Notably, Kumamoto et al. observed a significant therapeutic effect exclusively when employing MSCs cultured for 9 days, whereas cells subjected to a brief 2-hour adherence window failed to induce significant changes [45].

MSC administration consistently down-regulated lung TGF- β levels [46–48] and suppressed tumor necrosis factor- α (TNF- α) [49]. This includes a significant decrease in lung TGF- β protein expression and a reduction in lung TGF- β mRNA transcripts [40]. Pulmonary TNF- α dynamics were controversial in a few investigations. Moodley et al. demonstrated that amnion-derived MSCs (AMSCs) but not BM-MSCs, significantly decreased lung TNF- α protein levels [50], while their parallel study confirmed a significant reduction in TNF- α mRNA mediated by UC-MSCs [51]. Lee et al. found a significant reduction of the lung IL-1 levels at all measured time points up to day 28 in AMSC cohort [50], whereas UC-MSCs did not significantly alter lung IL-1 mRNA expression [51].

Additionally, Ganesan et al. (2023) found the robust therapeutic potential and mechanistic pathways of BM-MSCs using a topoisomerase I (TOPO I)-induced murine model of SSc-ILD [52]. MSCs exerted comparable suppressive effects on TOPO I-induced IgG1 and IgG2a production. Intravenous administration of MSC lineage significantly attenuated dermal thickening, reduced parenchymal fibrosis, and mitigated airway hyperresponsiveness.

An overview of the landmark preclinical studies evaluating the therapeutic utility of MSCs derived from diverse tissue niches is synthesized in Table 1.

BM- and AT-MSCs have been the most extensively studied MSC sources due to historical standardization (accounting for 54% and 21% of protocols, respectively), however, alternative sources - including UC-MSCs, amniotic (AMSCs), endometrial (EMSCs), and menstrual blood-derived stem cells (MenSCs) - demonstrate superior efficacy in reducing collagen deposition and restoring lung compliance [42]. This variability highlights the role of microenvironmental imprinting and niche-dependent properties, which dictate the specific secretome profiles of distinct MSC lines.

Mesenchymal stem cell-derived extracellular vesicles (MSC-EVs) therapy consistently mitigated the severity of pulmonary fibrosis [62]. Specifically, the intervention led to a marked downregulation of collagen deposition ($n = 10$ studies), α -SMA levels ($n = 5$ studies), hydroxyproline content ($n = 5$ studies), and pro-fibrotic TGF- β 1 signaling ($n = 6$ studies) relative to control cohorts [62].

The differentiation and anti-fibrotic capacity of MSCs is strictly governed by microenvironmental injury cues and remains highly time-dependent. Early administration (within 24 hours of lung injury) yields optimal results. Conversely, delaying transplantation by several days - when the acute pulmonary insult has already transitioned into established, chronic fibrotic remodeling - significantly attenuates the capacity of cells to arrest collagen deposition [42]. High-dose regimens ($\geq 1.0 \times 10^6$ cells per animal) and the intravenous delivery route demonstrate the most pronounced effect size, leveraging the systemic circulatory path to maximize cell homing to the damaged lung parenchyma.

This age-dependent potency parallels findings in radiation-induced pulmonary fibrosis models, where MSC delivery primarily mitigates pathology by dampening acute inflammation, impeding fibroblast proliferation/activation, and arresting collagen synthesis [63]. MSC transplantation suppresses fibroblast activation by upregulating the secretion of HGF and PGE2 (concurrently decreasing host expression of TGF- β 1 and TNF- α) [63].

It was found that donor senescence significantly compromises MSCs therapeutic efficacy [64]. Compared to aged counterparts (22 months), AT-MSCs harvested from young mice (4 months) markedly suppress interstitial and

Table 1

Preclinical (animal) studies of MSC therapy in lung fibrosis.

Injury model	MSC source	Outcome/ Main findings	Reference
CCl ₄ -induced pulmonary fibrosis	BM-MSCs of mice and rat	Reduced fibrosis, collagen deposition, inflammation, oxidative stress, and apoptosis; improved antioxidant enzyme activity.	[53]
Phosgene-induced acute lung injury	BM-MSCs of mice	Following transplantation, exogenously delivered MSCs selectively home to damaged pulmonary niches in phosgene-induced acute lung injury models. Once localized, they effectively restore alveolar-capillary barrier integrity and reduce epithelial hyperpermeability. This therapeutic stabilization is mediated by the capacity of MSCs to block TGF- β 1 and Wnt5a-driven inhibition, thereby rescuing and reactivating the vital Wnt3a/ β -catenin cytoprotective cascade.	[18, 54, 55]
Bleomycin-induced pulmonary fibrosis model	AT-MSCs of mice	MSC supernatant directly suppresses the TGF- β 1/Smad signaling cascade, thereby blocking TGF- β 1-induced differentiation of quiescent fibroblasts into contractile, matrix-secreting myofibroblasts. Concurrently, this acellular secretome stimulates fibroblast autophagy by strictly modulating the expression of the ubiquitin-binding scaffold protein p62, driving the clearance of aberrant cellular components and helping arrest the fibrotic cascade.	[56]
Bleomycin-induced pulmonary fibrosis model	AT-MSCs of mice	Intravascular administration of AT-MSCs significantly mitigated pulmonary fibrosis in mice. This improvement was evidenced histologically by reduced collagen deposition, lower hydroxyproline content, and the downregulation of key fibrotic markers, including Type I and III collagen genes and α -SMA.	[7]
IPF-humanized model (created by infusing human IPF-lung fibroblasts)	AT-MSCs of mice	Systemic MSC delivery successfully halted and improved fibrotic lung changes in these humanized mice	[7]
Bleomycin-induced pulmonary fibrosis model	human AT-MSC-derived exosomes were administered intranasally to mice.	AT-MSC-derived exosomes reduced lung inflammation, decreased infiltration of immune cells, and attenuated bleomycin-induced pulmonary fibrosis in mice. They also modulated Wnt/ β -catenin signaling and promoted tissue repair compared with bleomycin-treated controls.	[57]
bleomycin-induced pulmonary fibrosis model	AT-MSCs human-to-mouse	AT-MSCs exert potent immunomodulatory and anti-fibrotic effects in the lungs, providing maximum efficacy when deployed during the acute, initial phases of pathogenesis, effectively arresting early-stage inflammatory signaling and downstream matrix deposition prior to the establishment of widespread, irreversible parenchymal scarring.	[58]
bleomycin-induced pulmonary fibrosis model	AT-MSCs in rat model	AT-MSCs directly attenuate fibrotic cascades by Cav-1 expression and concurrently suppressing the NF- κ B signaling pathway. This dual molecular modulation inhibits the transcription and synthesis of collagen type I and hydroxyproline, while driving a robust downregulation of key pro-inflammatory and pro-fibrotic cytokines, specifically IL-6, IL-1 β , and TGF- β 1.	[59]
amiodarone induced pulmonary fibrosis	BM-MSCs and conditioned medium (CM) in a rat	MSCs transplantation demonstrated superior efficacy over CM in reversing amiodarone-induced pulmonary histopathological alterations. Sequential evaluations at 1, 2, and 4 months post-intervention revealed a time-dependent mitigation of fibroproliferative structural remodeling in both treatment cohorts, with BM-MSC delivery consistently yielding a more pronounced restoration of normal parenchymal architecture relative to acellular CM therapy.	[60, 61]
topoisomerase I induced SSc-ILD-like model	allogeneic and syngeneic BM-MSCs	MSCs exerted comparable suppressive effects on TOPO I-induced IgG1 and IgG2a production. Intravenous administration of MSC lineage significantly attenuated dermal thickening, reduced parenchymal fibrosis, and mitigated airway hyperresponsiveness.	[52]

perivascular collagen deposition while downregulating key profibrotic markers, including TGF- β , MMP-2, and protein kinase B (Akt) [64].

Unmodified MSCs often face challenges like poor persistence and engraftment within the inflammatory and fibrotic microenvironment of a fibrotic lung. Pretreatments (or preconditioning) are designed to educate the cells and boost their efficacy prior to administration. Culturing MSCs in low-oxygen conditions prior to transplant increases their survival rate, upregulates their anti-inflammatory secretions, and helps modulate collagen deposition in lung [22]. Pretreating MSCs with KGF or Oncostatin M has been shown to boost the cells' ability to home into fibrotic tissue and upregulates HGF secretion [22].

Beyond ex vivo preconditioning, integrating genetic engineering with stem cell biology offers substantial therapeutic potential for mitigating fibrotic lung pathologies. In experimental models of silicon dioxide-induced pulmonary fibrosis, transplantation of allogeneic BM-MSCs modified to overexpress BMP-7 successfully arrested fibrotic progression by suppressing the EMT cascade [65]. These genetically engineered cellular lines demonstrate superior antifibrotic efficacy compared to native,

unmodified BM-MSCs. Furthermore, transducing MSCs with vectors encoding IL-10 or HGF effectively counteracts potential treatment-induced adverse effects—specifically mitigating risks associated with anomalous or excessive endogenous secretion of TGF- β by the transplanted cells [66].

The vast majority of in vivo animal studies rely on acute lung injury models where MSC administration occurs during the initial inflammatory phase rather than in established, chronic parenchymal fibrosis. Consequently, these models reflect protection against acute injury rather than the reversal of established matrix deposition characteristic of advanced PPF.

Clinical Experience and Ongoing Trials

Published clinical trials sourced from ClinicalTrials.gov and PubMed with the combination of keywords, including “PPF”, “IPF”, “ILD”, “pulmonary fibrosis”, and “MSC”, uniformly confirm that MSC administration is safe for select patient cohorts. Human clinical data on MSC therapy in PPF remain limited (Table 2). Consequently, current evidence is derived predominantly from studies conducted in patients with IPF, which provide important safety and feasibility

Table 2

Overview of recent clinical studies of MSC therapy in patients with progressive pulmonary fibrosis.

ClinicalTrials.gov (ID Number)	Intervention/treatment	Dosage	Participants number	Results	Reference
NCT02013700	Allogeneic adult human MSCs/ matched placebo	20, 100, or 200*10 ⁶	9	Over 60 weeks following infusion, mean % predicted FVC decreased by 3.0%, accompanied by a 5.4% reduction in mean % predicted DLCO.	[67]
NCT01919827	Endobronchial infusion of autologous BM-MSCs	10 × 10 ⁶ , 50 × 10 ⁶ and 100 × 10 ⁶	17	The main group experienced an initial 8.1% decrease in mean FVC at 3 months. While 46% of patients managed to avoid functional decline early on, only 23% maintained that stability by month 12.	[68]
NCT02594839	Allogeneic MSCs transplantation	two doses of 2 × 10 ⁸ MSCs every 3 months - a total of 1.6 × 10 ⁹ MSCs	20	For the MSCs treatment group: FVC actively improved from a baseline decline of -13.8% to a positive gain of +3.7%. For the placebo group: FVC continued its downward trajectory, showing virtually no meaningful recovery (moving from -11.7% to -9.5%).	[69]
NCT01385644	Placental Mesenchymal Stem Cells	1 -2 × 10 ⁶ MSC/kg	8	At the 6-month mark, there was basically no change from baseline. Lung function (FVC and DLCO), walking endurance (6MWD), and CT scans all remained steady. No evidence of increased fibrosis was detected. Intravenous MSC treatment appeared safe in the short term for patients with moderately severe IPF.	[70]
NCT07131150	Menstrual Blood-Derived MSCs	Group 1: 3 × 10 ⁷ cells every 3 days, with a total dose of 9 × 10 ⁷ cells; Group 2: 3 × 10 ⁷ every day with the total dose 1.8 × 10 ⁸ cells	66	Not yet recruiting	Not posted
NCT05468502	Allogeneic hUC-MSCs	a single dose of 6.0 × 10 ⁶ , 3.0 × 10 ⁷ , 6.0 × 10 ⁷ , and 1.2 × 10 ⁸ cells / person	18	Not yet recruiting	Not posted
NCT05016817	Allogeneic hUC-MSCs	1 × 10 ⁸ cells	20	Not yet recruiting	Not posted
NCT03929120	Allogeneic BM-MSCs	0.5 -1 × 10 ⁶ cells/kg	10	Not yet recruiting	Not posted
NCT02135380	Autologous AT-MSCs	Not available	60	Not yet recruiting	Not posted

data but cannot be directly extrapolated to the broader PPF population.

Four completed early-phase trials have published findings confirming the safety and procedural feasibility of MSC protocols in IPF cohorts. Phase I/II trial investigating AT-MSCs in IPF (NCT02135380), allogeneic UC-MSCs (NCT05468502, NCT05016817), menstrual blood-derived MSCs (NCT07131150) and BM-MSCs (NCT03929120) remains uncompleted, with no recent status updates.

A randomized, placebo-controlled trial evaluated allogeneic bone marrow MSCs at a cumulative dose of 1.6 × 10⁹ cells delivered intravenously over 12 months (2 × 10⁸ cells every 3 months) in twenty patients with PPF [69]. Treatment demonstrated an excellent safety profile with no significant adverse reactions. MSC intervention : was associated with favorable trends in the 6-minute walk distance (6MWD) at week 13, followed by a rise in DLCO at week 26 and FVC at week 39 compared to placebo [69]. However, given the small sample size and exploratory nature of the study, these findings should be interpreted as preliminary signals of potential efficacy rather than definitive evidence of clinical benefit.

A single infusion of allogeneic human MSCs in cohorts with mild-to-moderate IPF demonstrated a favorable safety profile, showing no treatment-emergent serious adverse events, including nonfatal pulmonary embolism, cerebrovascular accidents, acute respiratory hospitalizations, or severe laboratory toxicities [67]. Patients receiving MSC therapy demonstrated numerically more stable pulmonary function parameters than those receiving placebo; however, the study was not powered to establish clinical efficacy [6]. These

findings reinforce the safety, tolerability, and potential clinical benefit of higher-dose MSC therapy and provide preliminary evidence warranting further evaluation in adequately powered clinical trials.

Intravenous administration of placenta-derived MSCs in patients with moderately severe IPF demonstrates good tolerability and a favorable short-term safety profile in a small early-phase study. Treatment-related adverse events were limited to mild, self-resolving effects, such as a transient decline in oxygen saturation shortly after infusion and no significant hemodynamic changes. Over a 6-month follow-up period, lung function parameters (FVC, DLCO), exercise capacity (6MWD), and CT fibrosis scores remained stable, with no evidence of disease worsening [71]. However, the small sample size limit conclusions regarding efficacy.

A primary limitation of systemic MSC therapy is that the physical properties of these cells rarely allow them to successfully engraft at the actual injury site, which severely restricts their therapeutic impact. To circumvent systemic entrapment and optimize localized cell homing to active fibrotic niches, alternative delivery strategies have been evaluated, including endobronchial instillation of MSCs. This method demonstrated an absence of acute infusional toxicities or late-onset ectopic tissue differentiation [71]. Another MSC delivery method utilizes the nebulization of stem cells into respirable aerosols, administered to patients via an inhalation mask. By employing an aerosolized route, this approach bypasses the primary clinical complications associated with traditional intravenous administration, including first-pass pulmonary capillary entrapment, poor trans-endothelial extravasation into the interstitial space, and infusional

thromboembolism risk. However, the practical application of this methodology is constrained by the requirement for highly specialized formulation chemistry and sophisticated aerosol generation systems to preserve cellular viability during shear stress [72].

Since Friedenstein et al. first isolated BM-MSCs in 1970, they have served as the standard multipotent cell source for both preclinical and clinical transplantation (Tab.3). However, BM-MSC harvesting is highly invasive, painful, and poses viral risks. Furthermore, donor aging significantly compromises their quantity, differentiation capacity, and overall longevity [6]. By comparison, UC-MSCs provide a comparable therapeutic profile while bypassing these limitations; they are non-invasively harvested, ethically uncontroversial, and exhibit superior self-renewal rates [41].

Nowadays, among the diverse sources of mesenchymal stem cells, BM-MSCs, UC-MSCs, and AT-MSCs have shown

broadly comparable protective effects and have been used in research on pulmonary fibrosis due to their abundant availability, capacity for regeneration, and ability to modulate the immune response (Tab.3). From a clinical perspective, AT-MSCs may represent an attractive candidate considering minimally invasive harvesting procedures and carry fewer ethical constraints than other stem cell sources [7]. Placental and amniotic membrane-derived mesenchymal stem cells (PMSCs and AMSCs) represent promising birth-tissue sources for cell therapy in PPF (Tab.3). Isolated from placenta or amniotic membrane post-partum without donor risk or invasive surgical procedures, these cells possess low immunogenicity (low expression of MHC Class I, absence of Class II (HLA-DR) and co-stimulatory molecules (CD80, CD86) [71]. They demonstrated high proliferative potential and a robust paracrine secretome rich in pro-angiogenic, anti-apoptotic, and immunomodulatory factors (Tab.3). Intravenous PMSCs administration at the

Table 3 **Comparative analysis of mesenchymal stem cell (MSC) sources in pulmonary fibrosis research.** AT-MSCs - adipose-tissue derived mesenchymal stem cells; AMSCs - amniotic mesenchymal stem cells; BM-MSCs - bone marrow-derived mesenchymal stem cells; EMT -epithelial-mesenchymal transition; MFGES - milk fat globule-EGF factor 8; PMSCs - placental mesenchymal stem cells; UC-MSCs - umbilical cord-derived mesenchymal stem cells.

BM-MSCs		AT-MSCs	UC-MSCs	PMSCs / AMSCs
Primary mechanisms of action	Downregulation of TGF-β1/Smad3 pathway; attenuation of alveolar epithelial cell apoptosis; suppression of myofibroblast differentiation.	Paracrine suppression of pro-fibrotic cytokines; activation of autophagy via p62/mTOR modulation; Cav-1/NF-κB pathway inhibition.	Secretome-mediated inhibition of collagen I/III synthesis; upregulation of MFGES; M2 macrophage polarization.	Paracrine suppression of TNF-α and IL-1β; preservation of alveolar-capillary barrier integrity; inhibition of EMT.
Key advantages	Extensively characterized gold standard in cell therapy; well-established isolation and expansion protocols; strong historical safety profile.	Abundant tissue source; accessible via minimally invasive liposuction; high primary cell yields and robust in vitro proliferation.	Non-invasive, ethically unconstrained procurement from birth waste; high proliferation rate; lower immunogenicity (low HLA-DR expression).	Plentiful birth-tissue source; no invasive donor procedures; strong immunomodulatory and paracrine secretome profile.
Biological and practical limitations	Invasive and painful bone marrow aspiration; age-dependent decline in cell yield, differentiation, and potency; donor senescence.	Donor-to-donor variability influenced by age, BMI, and metabolic state; variable secretome quality depending on isolation method.	Dependent on tissue banking infrastructure; limited potential for autologous application; requires strict donor screening protocols.	Heterogeneity across isolation protocols; variable cell phenotypes depending on maternal vs fetal tissue origin.
Feasibility and safety	Evaluated in early-phase trials via intravenous delivery (e.g., AETHER trial, NCT02013700). Demonstrates short-term infusional safety and tolerability; efficacy outcomes remain exploratory and unproven.	Evaluated via endobronchial and intravenous routes (e.g., NCT01919827). Confirms short-term feasibility; no conclusive evidence of lung function stabilization or disease reversal.	Currently under investigation in Phase I/II safety studies (e.g., NCT05468502, NCT05016817). Shows high short-term tolerability; long-term functional durability remains unverified.	Evaluated in Phase Ib safety trials (e.g., NCT01385644). Confirms short-term infusional safety; exploratory endpoints (FVC, DLCO) show no statistically significant disease modification.

dose of 1-2×10⁶ demonstrated good short-term safety profile and unchanged FVC, DLCO, and 6MWD at 6 months period [71].

Clinical and preclinical protocols evaluate highly heterogeneous MSC dosing concentrations. Comparative studies have suggested a possible association between higher cell doses and greater physiological responses, though they correlate with a higher incidence of transient, self-limiting infusional adverse events, such as pyrexia and rigors [73]. Furthermore, the anatomical source of the MSCs dictates the maximum attainable cellular yield for clinical administration. BM-MSCs accommodate the widest therapeutic range, with administered doses spanning from 1×10⁷ to 1.6×10⁹ total cells, while UC-MSCs are typically restricted to absolute concentrations ranging between 5×10⁶ and 5.5×10⁷ cells [73]. Weight-adjusted dosing models are utilized for other birth-tissue and stromal lines: placenta-derived MSC protocols deploy weight-dependent concentrations of 1-2×10⁶ cells/kg of body weight, whereas AT-MSCs regimens are standardized at approximately 1.5×10⁶ cells/kg of body weight [70, 74].

Recent research has shifted toward MSC-derived extracellular vesicles as a cell-free alternative for treating tissue fibrosis. These EVs range from 30 to 5,000 nm in diameter and are classified according to their size and biogenesis as exosomes (30–100 nm), which originate via the endocytic pathway, microvesicles or ectosomes (100–1,000 nm), which arise through plasma membrane budding, and apoptotic bodies (100–5,000 nm), formed during apoptosis [6, 75]. Functionally, EVs act as vehicles transporting diverse cargo, such as mRNAs, microRNAs, enzymes, and other bioactive molecules [75]. While the specific impact of MSC-EVs on IPF remains an emerging field with limited literature, key mechanisms have recently been identified. Mansouri et al. (2019) demonstrated that MSC-EVs modulate the pulmonary immune environment by shifting classical/pro-inflammatory monocytes, non-classical monocytes, and alveolar macrophages toward a protective phenotype [76].

Overall, current clinical evidence for MSC therapy in pulmonary fibrosis remains limited to small early-phase studies primarily designed to evaluate safety and feasibility. Although

some studies have reported favorable trends in functional and physiological outcomes, the limited sample sizes and heterogeneity of study designs preclude definitive conclusions regarding efficacy.

Discussion

Progressive pulmonary fibrosis represents a major cause of morbidity and mortality in ILD and connective tissue diseases. Despite the established clinical use of conventional antifibrotic agents, therapy frequently fails to halt disease progression. Recent insights into the pathophysiological mechanisms driving PPF have resulted in the creation of innovative treatment approaches, initiating the development of next-generation interventions currently undergoing clinical evaluation. While early-phase trials demonstrate encouraging safety and efficacy profiles, there is an urgent clinical imperative to identify alternative strategies capable of targeting the multifaceted nature of fibrogenesis.

Cumulative preclinical and clinical evidence underscores the potent immunomodulatory, anti-inflammatory, and anti-fibrotic effects of MSCs, establishing them as promising candidates for regenerative medicine. MSC transplantation improves overall survival rates and attenuates histological lung fibrosis scores in experimental models of pulmonary fibrosis. Preclinical studies validate the anti-fibrotic potential of the MSC and its secretome in animal models. However, because the majority of these animal models administered cells during the acute inflammatory cascade rather than during established fibrogenesis, the evidence mainly supports the use of MSCs for managing acute exacerbations of IPF, rather than reversing chronic fibrotic disease [40].

Accumulating evidence supports MSCs as a multipronged therapeutic strategy targeting the inflammatory and fibrotic cascades. Their low immunogenicity, high proliferation potential, and broad availability make them suitable for allogeneic use. However, a prominent gap in contemporary literature is the scarcity of robust, long-term safety data considering variability in cell sources and manufacturing standards (GMP compliance). While clinical trial data confirm the short-term safety of MSCs in IPF [67], the long-term fate of these entrapped cells remains largely unknown. Given the unpredictable and progressive nature of PPF, comprehensive monitoring is essential to exclude late-onset adverse events, ectopic tissue differentiation, or paradoxically accelerated fibrotic responses before these protocols can be integrated into routine clinical workflows.

Significant experimental variability across preclinical studies hinders direct data synthesis and clinical translation. Existing literature spans diverse animal species (primarily mice and rats) and non-standardized injury models, including bleomycin, phosgene, amiodarone, carbon tetrachloride, and topoisomerase I induction. Protocols further diverge across cell sources (BM, UC, AT, and amnion), donor origins (allogeneic versus syngeneic), dosing scales (1×10^5 to 1×10^6 cells per animal), and delivery pathways (intravenous, endobronchial, or intranasal). Inter-study timing ranges from hyperacute administration to delayed interventions, while primary endpoints rely on disparate combinations of histological scores, collagen content, survival, and cytokine profiles. These methodological discrepancies prevent direct quantitative comparison and complicate the derivation of standardized parameters for human clinical trials.

The therapeutic value is robust, often reflecting more than a three-fold elevation in the odds of survival in comparison with untreated controls, supported by highly consistent inter-

study heterogeneity. Emerging preclinical strategies utilizing genetic modification (overexpressing specific cytoprotective or anti-inflammatory genes) or ex vivo preconditioning (hypoxia, cytokine priming) represent the next translational frontier to enhance cell survival and efficacy within the hostile, oxidative microenvironment of the fibrotic lung.

The marked disparity between robust anti-fibrotic efficacy in preclinical studies and modest functional signals in early-phase clinical trials represents a critical translational challenge in regenerative pulmonology. Standard rodent models including single-dose intratracheal bleomycin induce acute, reversible toxic lung injury with peak inflammation at days 3–7, followed by transient matrix deposition that spontaneously resolves by days 28–35. In contrast, human PPF are chronic, non-resolving disorders driven by repetitive epithelial micro-injury, aberrant repair, and progressive ECM cross-linking without a primary acute inflammatory phase.

A critical factor in interpreting preclinical outcomes is the timing of cell delivery relative to disease progression. Most animal models administered MSCs during the early inflammatory phase following acute lung injury (typically within 24 to 72 hours post-induction). Consequently, these studies predominantly evaluated the prevention of early fibrotic onset by dampening acute inflammatory cascades and preliminary matrix deposition, rather than the reversal of established, chronic parenchymal fibrosis. In contrast, clinical trials enroll patients with established parenchymal remodeling, where anti-inflammatory mechanisms exert negligible impact on cross-linked collagen or active fibroblastic foci.

Rodent models employ dosages of 1×10^5 to 1×10^6 cells per animal, translating to weight-adjusted scales of 5×10^6 to 20×10^6 cells/kg. However, human clinical protocols cap systemic dosing at 1.5×10^6 to 2.5×10^6 cells/kg due to concerns regarding microvascular embolization and safety limits.

Intravenously administered MSCs undergo immediate sequestration in the pulmonary microvasculature ("first-pass effect"). In human fibrotic lungs characterized by microvascular rarefaction, capillary obliteration, and elevated local oxidative stress, trapped MSCs exhibit accelerated apoptosis, shortening their paracrine window compared to healthy or acutely injured animal models.

Preclinical experiments utilize young, inbred, pathogen-free rodents. Clinical cohorts consist of older individuals with advanced cellular senescence, persistent telomere attrition, and altered systemic inflammatory baselines.

Animal studies evaluate treatment response via destructive tissue assays, including Ashcroft histological scoring, lung hydroxyproline content, and total collagen quantification. Furthermore, human trials rely on non-invasive physiological surrogate markers, primarily FVC, DLCO, and 6MWD. Spirometric measures reflect global, irreversible structural changes, localized paracrine modulation of alveolar microenvironments by transiently surviving MSCs is insufficient to induce measurable physiological shifts over short trial horizons (3–12 months).

Alternative delivery routes also warrant caution; for instance, while endobronchial instillation of BM-MSCs did not trigger immediate severe adverse events, a notable proportion of patients exhibited subsequent clinical and functional decline. Furthermore, identified risks of genomic instability in BM-MSCs during protracted ex vivo expansion raise substantial safety concerns regarding the autologous application of MSCs in elderly or severely compromised IPF cohorts [77]. To bypass these cellular limitations, the paradigm of cell-free therapy using

MSC-derived EVs is particularly attractive, offering reduced immunological risks and improved scalability.

Because the vast majority of preclinical and clinical trials evaluating MSC therapy have been conducted exclusively in IPF cohorts or acute bleomycin models, extrapolating these safety and efficacy profiles to non-IPF PPF phenotypes carries inherent uncertainty. Non-IPF fibrotic ILDs encompass distinct immune drivers and tissue dynamics that differ significantly from IPF. Consequently, findings derived from IPF-centric studies should not be assumed to be directly applicable across all PPF subtypes until targeted clinical trials in specific non-IPF cohorts are completed.

When patients with PPF secondary to ILD experience functional failure on first-line antifibrotics (such as nintedanib or pirfenidone), downstream therapeutic pathways become profoundly constrained, leaving supportive oxygen therapy, pulmonary rehabilitation, and palliative care [78]. In this specific cohort of patients, MSC transplantation should be evaluated not as a curative modality, but rather as a strategic intervention aimed at functional stabilization. By targeting the chronic alveolar inflammation, cell-based therapy has the potential to slow down the decline in FVC, thereby extending the therapeutic window and prolonging the period prior to definitive lung transplantation.

Early-phase clinical trials evaluating intravenous and endobronchial delivery of allogeneic or autologous MSCs report a consistent short-term safety profile. Systemic administration of MSC at cumulative doses up to 1.6×10^9 cells showed no acute dose-limiting toxicities, anaphylactic responses, or treatment-related mortality [79]. Observed secondary events were transient and mild, consisting primarily of low-grade post-infusion pyrexia, minor chest discomfort, and transient fluctuations in peripheral oxygen saturation [73]. No ectopic tissue formation or cellular transformation was reported within published monitoring windows [69, 79, 80].

Existing clinical evaluations of MSC transplantation in fibrotic interstitial lung disease remain restricted to early-phase (Phase I/II) trials with small sample sizes, brief follow-up durations, and notable cohort heterogeneity regarding underlying etiologies, dosing regimens, cell origins, and delivery routes. Enrolled populations span diverse underlying ILD etiologies, varying baseline lung function impairments, and differing rates of prior disease progression. Clinical protocols lack standardization in cell dosing (ranging from 5×10^6 to 1×10^9 total cells or weight-adjusted equivalents) and administration routes (intravenous vs. endobronchial). Endpoints focus heavily on exploratory biomarkers and short-term functional markers (FVC, DLCO, 6MWD) over brief follow-up periods (3–12 months), leaving long-term efficacy, functional durability, and late-onset safety uncharacterized. Larger, randomized, double-blind, phase II/III controlled trials are needed to determine whether the profound anti-fibrotic mechanisms documented in vivo translate into meaningful clinical benefit in humans, establish long-term efficacy and functional durability. Future

research must standardize production variables, including cellular source, isolation protocols, and optimal delivery routes, to confirm safety in human clinical trials.

Ultimately, integrating these advanced cellular and cell-free therapies into the routine pulmonology practice requires a rigorous, multi-tiered regulatory infrastructure.

Conclusions

Preclinical data and early-phase clinical trials consistently confirm the short-term safety and immunomodulatory potential of MSC therapy in progressive pulmonary fibrosis. However, robust evidence demonstrating clinical efficacy remains lacking due to small sample sizes, study heterogeneity, and brief follow-up periods across current trials. Major translational challenges persist, including uncertain long-term cellular fate, unstandardized dosing and delivery protocols, and an incomplete understanding of optimal administration windows. Transitioning MSC therapy from experimental models into routine clinical practice will require adequately powered, randomized controlled trials alongside standardized manufacturing standards, unified patient selection criteria, and clear regulatory oversight to definitively establish long-term safety, functional durability, and therapeutic efficacy.

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