Stem Cell Research & Therapy

CORRESPONDENCE Open Access

Stem cell therapies for pulmonary fibrosis: emerging hope through ongoing challenges

Hanyu Shi[1], Ruihui Geng[1] and Hui Liu[2*]

Abstract
Stem cell therapy represents an emerging intervention for pulmonary fibrosis (PF), a severe lung disease lacking effective treatments. We conducted a systematic retrospective review of stem cell clinical trials for PF registered up to the end of 2024, utilizing the Trialtrove database alongside other registries.

Keywords Stem cell, Pulmonary fibrosis, Clinical trial

Pulmonary fibrosis is a progressive lung interstitial disease driven by pathological activation of myofibroblasts and disrupted extracellular matrix architecture. These alterations contribute to poor prognosis and limited treatment alternatives. Lung transplantation offers the only curative option available for severe PF, though its application is limited due to donor scarcity and eligibility criteria, underscoring the need for new treatment approaches [1]. Stem cells, endowed with self-renewal and multipotent differentiation capacities across various lineages—including adipocytes, epithelial cells, and myocytes—have attracted considerable interest in regenerative medicine. Recent clinical trials increasingly explore their potential in PF treatment, reflecting a promising therapeutic avenue [2].

To comprehensively evaluate the efficiency and tolerability of stem cell therapies in patients affected by pulmonary fibrosis, we conducted a systematic search of clinical trials using the Trialtrove database (https://clinicalintelligence.citeline.com). We employed a multi-step search strategy, initially extracting trials with drug type labeled as "cell type," specifically stem cells, in conjunction with a full-text search for "stem cell" or "stem cells," followed by intersection with the pulmonary fibrosis therapeutic area. As of December 31, 2024, an initial 84 trials were retrieved, of which 57 met our inclusion criteria following manual review. To ensure completeness, we cross-checked these findings against ClinicalTrials.gov, the Chinese Clinical Trial Registry (ChiCTR), and the European Medicines Agency (EMA) online database, which yielded two additional trials from ClinicalTrials.gov and three more from other registries not covered by Trialtrove. After removing duplicates, a total of 62 trials were finally included for the analysis (Figure S1).

Between 2000 and 2007, the number of clinical trials was comparatively low. However, a significant increase in trial registrations was observed during the period from 2008 to 2011 and continued steadily through 2016 to 2023 (Fig. 1A). Among the 62 trials identified, the majority were conducted by academic research institutions (Fig. 1B), with 41.9% taking place in China, followed by the United States (14.5%) and Japan (9.6%, Fig. 1C). As illustrated in Fig. 1D and Table S1, most studies are in the early phases of development, with exploratory, phase I, and phase II trials comprising 91.9% of the total. In contrast, only a small fraction of trials has advanced to phase III (3.2%) and phase IV (4.8%). The majority of these

*Correspondence:
Hui Liu
lh00912@126.com
[1]Department of Internal Medicine, Hospital of the First Mobile Corps of the Chinese People's Armed Police Force, Dingzhou 073099, Hebei, China
[2]Department of Weigongqiao Outpatient, Jingxi Medical Section of PLA General Hospital, 1#, West Third Ring Road, Beijing 100089, China

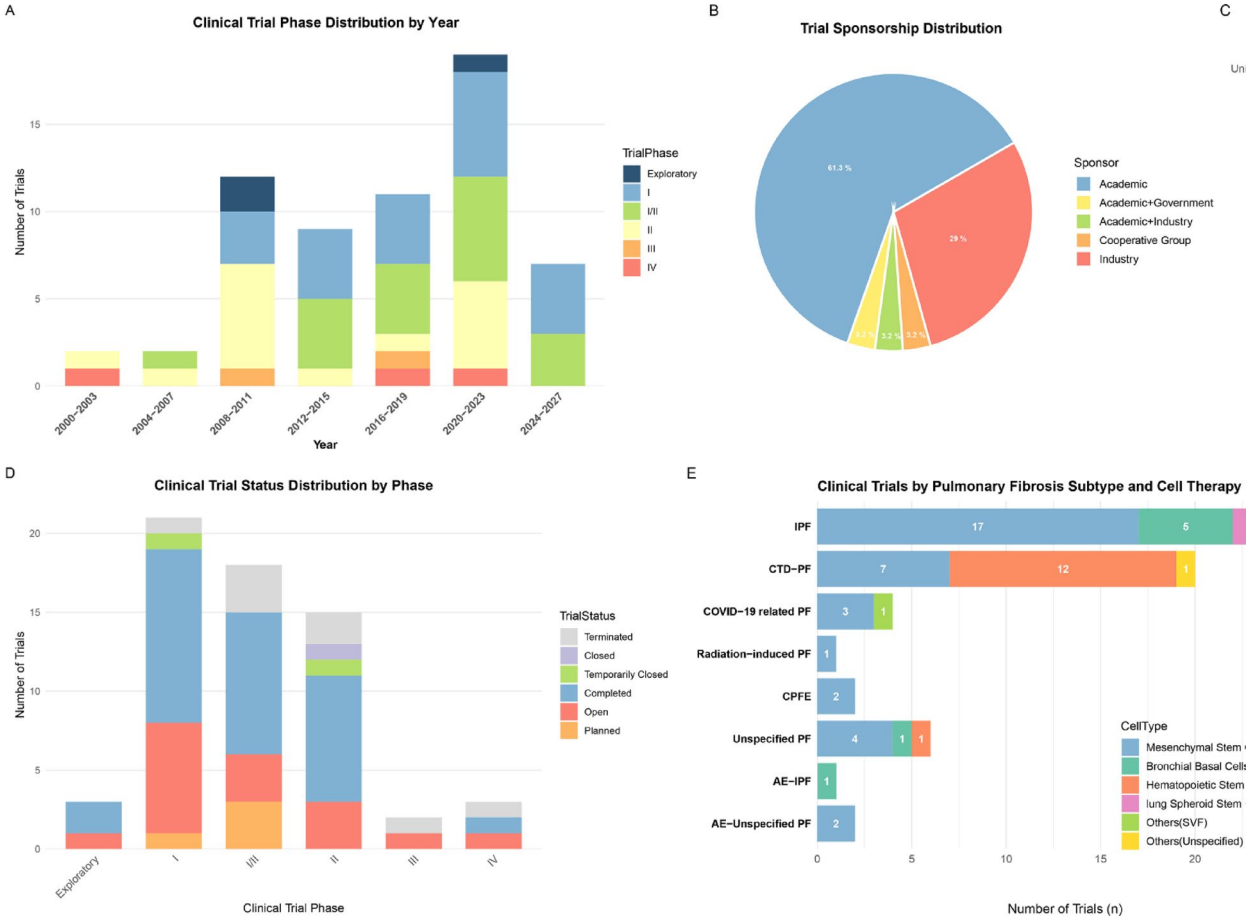

Fig. 1 Global landscape of stem cell therapy trials in pulmonary fibrosis. **A** Distribution of clinical trials by study phase over time. **B** Sponsorship distribution of included clinical trials. **C** Geographic distribution of clinical trials by country. **D** Clinical trial status stratified by phase. **E**. Distribution of clinical trials according to pulmonary fibrosis subtypes and stem cell therapy types. **F** Sankey diagram illustrating the flow of completed trials categorized by disease subtype, cell therapy type, and clinical trial phase. IPF, idiopathic pulmonary fibrosis; CTD-PF, connective tissue disease-associated pulmonary fibrosis; CPFE, combined pulmonary fibrosis and emphysema; AE-IPF, acute exacerbation of IPF; MSCs: mesenchymal stem cells, BSCs, bronchial basal cells; HSC, hematopoietic stem cell; LSC, lung spheroid cell; SVF, stromal vascular fraction; iPSC, induced pluripotent stem cell

studies have focused on idiopathic pulmonary fibrosis (IPF) and connective tissue disease-related pulmonary fibrosis (CTD-PF). Most research targeted mesenchymal stem cells (MSCs, 72.5%), while hematopoietic stem cells (HSCs) were mainly conducted for CTD-PF treatment (Fig. 1E).

MSCs (or more accurately, mesenchymal stromal cells/multipotent mesenchymal stromal cells), the most widely applied stem cell type, mitigate pulmonary fibrosis primarily through modulating the immune response by reducing pro-inflammatory cytokines and promoting anti-inflammatory macrophages. They inhibit fibrosis by suppressing epithelial-mesenchymal transition (EMT), decreasing collagen and fibronectin deposition, and balancing metalloproteinases (TIMPs) and matrix metalloproteinases (MMPs) [3]. Based on completed trial results (Fig. 1F and Table S1), MSCs demonstrated good tolerability in both IPF and CTD-PF patients, with no serious adverse events reported. Furthermore, MSC treatment was associated with notable improvements in clinical symptoms and pulmonary function [2]. HSCs, applied exclusively in CTD-PF studies, suggested improved event-free survival at 48 months alongside enhanced Health Assessment Questionnaire Disability Index (HAQ-DI) scores after two years. However, patients receiving HSC therapy also experienced a significantly higher incidence of severe adverse events, comparable to those observed with cyclophosphamide treatment [4]. In addition, administration of stromal vascular fraction (SVF), a heterogeneous cell population derived from adipose tissue that exhibits characteristics similar to bone marrow-derived mesenchymal stem cells (BM-MSCs), was reported to be well tolerated in a small safety study involving mild IPF patients, with no clinically significant adverse events and some improvement in quality of life [5]. Nonetheless, evidence remains limited to this initial trial, with no subsequent efficacy studies or long-term outcome data available. Accordingly, while SVF therapy

shows preliminary safety, its actual clinical benefit for IPF requires further investigation. Similarly, treatment with bronchial basal cells (BSCs) indicated a favorable safety profile in patients with acute exacerbation of IPF (AE-IPF), with fever being the most frequently observed adverse event [6].

Geographical disparities in clinical trials may reflect differences in regulatory frameworks and research priorities. While the United States accounts for 43% of global stem cell research, pulmonary fibrosis trials demonstrate that China surpasses both the US and Spain in terms of trial phases, stem cell types used, and sponsorship. This trend, alongside China's prominent role in induced pluripotent stem cell (iPSC) research [7], likely reflects a more permissive regulatory environment that encourages innovation, contrasting with the more safety- and ethics-focused regulations in the US and European Union. It is also noteworthy that despite India's strict regulatory guidelines, literature indicates challenges in enforcement, with numerous studies offering unproven therapies [8]. The termination of a trial (TrialTroveID-192528) observed in this analysis may underscore ongoing regulatory challenges.

Emerging advances in stem cell therapy emphasize the integration of nanotechnology and combination antifibrotic pharmacotherapy to enhance clinical efficacy. Among these advances, one study constructed a platform combining MSCs with type I collagenase-modified lipid vesicles loaded with nintedanib (MSCs-Lip@NCAF), which selectively targets fibrotic lung tissue. These lipid vesicles release nintedanib in response to matrix metalloproteinase-2 (MMP-2) sensitivity, facilitating the degradation of collagen fibers and targeted delivery of the drug to fibroblasts. The results demonstrated that MSCs-Lip@NCAF not only reversed pulmonary fibrosis in young mice but also showed therapeutic potential in aged mice (16 months old) with severe fibrosis [9]. However, this promising approach remains limited to animal models, and its translation into human clinical trials warrants further investigation.

Although anti-fibrotic agents such as nintedanib and pirfenidone are standard treatments for IPF, their efficacy is modest and side effects—including nausea and diarrhea—often compromise patient adherence. Recent findings from the phase III FIBRONEER-IPF trial suggest that the PDE4B inhibitor nerandomilast can significantly slow the decline in forced vital capacity (FVC) in IPF patients while maintaining acceptable safety and tolerability [10]. Nerandomilast inhibits the pro-fibrotic cytokine TGF-β through activation of the cAMP signaling pathway, thereby reducing inflammation and fibrosis [11]. Meanwhile, MSCs reduce inflammation by secreting TGF-β inhibitors and demonstrate enhanced reparative efficacy in attenuated inflammatory environments [3]. Based on these, we preliminarily propose that nerandomilast's modulation of the inflammatory microenvironment may create optimal conditions that facilitate MSC-driven tissue regeneration.

Another promising future direction is the development of induced pluripotent stem cells (iPSCs). Since firsted reported by Takahashi in 2006, iPSCs have been valued for their self-renewal and pluripotency, allowing differentiation into various cell types, including lung epithelial cells such as alveolar type II (ATII) and progenitor cells [12]. Unlike MSCs, which mainly modulate immunity and inflammation, iPSCs not only share these functions but also directly promote tissue regeneration to prevent fibrosis. For instance, transplantation of differentiated ATII cells derived from iPSCs in bleomycin-induced pulmonary fibrosis mice has been shown to suppress fibrotic markers such as TGF-β and α-smooth muscle actin (α-SMA), restore alveolar epithelium and extend survival [13]. However, it is important to note the potential tumorigenic risk associated with iPSCs, requiring improved differentiation protocols to enhance safety. Non-viral and site-specific targeting methods have shown promise in reducing such risks [3, 12]. In addition, clinical data on iPSC therapy for pulmonary fibrosis are still limited, necessitating further studies to confirm efficacy and safety.

In conclusion, the past decades have witnessed substantial global growth in clinical trials exploring stem cell-based therapies for pulmonary fibrosis, offering promising new treatment options and research pathways. While this area remains in the initial stages of clinical investigation, existing studies have provided preliminary evidence supporting both the safety and effectiveness of these approaches. Moving forward, enhancing clinical trials through global, multicenter partnerships will expand research applicability and support tailored treatments for diverse patient groups.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13287-025-04765-w.

Supplementary Material 1

Supplementary Material 2

Acknowledgements

We thank everyone of the team for the completion of the manuscript. The authors declare that they have not use AI-generated work in this manuscript.

Author contributions

Hanyu Shi and Hui Hui conceived and designed the study, drafted the original manuscript, and revised and edited it. Ruihui Geng contributed to the design and revision of the figures. All authors have reviewed and approved the final manuscript for publication and agree to be accountable for all aspects of the work.

Funding
This work was supported by Independently Developed Research Project of the Chinese Armed Police (ZZKY20243122) and Military Special Healthcare Research Project (24BJZ36).

Data availability
All the source data in this work are derived from clinical trial publicity platforms. The datasets analyzed during the study are available from the manuscript and supplement materials.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Yes.

Competing interests
The authors declare no competing interests.

Received: 1 June 2025 / Accepted: 20 October 2025
Published online: 26 January 2026

References

1. Koudstaal T, et al. Pulmonary fibrosis: from pathogenesis to clinical decision-making. Trends Mol Med. 2023;29(12):1076–87.
2. Chen S, et al. The efficacy of mesenchymal stem cells in bronchiolitis obliterans syndrome after allogeneic HSCT: A multicenter prospective cohort study. eBioMedicine. 2019;49:213–22.
3. Cheng W, Zeng Y, Wang D. Stem cell-based therapy for pulmonary fibrosis. Stem Cell Res Ther. 2022;13(1):492.
4. Bruera S, et al. Stem cell transplantation for systemic sclerosis. Cochrane Database Syst Rev. 2022;7(7):Cd011819.
5. Tzouvelekis A, et al. A prospective, non-randomized, no placebo-controlled, phase Ib clinical trial to study the safety of the adipose derived stromal cells-stromal vascular fraction in idiopathic pulmonary fibrosis. J Transl Med. 2013;11:171.
6. Zhang S, et al. Autologous P63 + lung progenitor cell transplantation in idiopathic pulmonary fibrosis: a phase 1 clinical trial. eLife. 2025;13:RP102451.
7. Song SJ, et al. Comparative analysis of regulations and studies on stem cell therapies: focusing on induced pluripotent stem cell (iPSC)-based treatments. Stem Cell Res Ther. 2024;15(1):447.
8. Tiwari SS, Desai PN. Unproven stem cell therapies in india: regulatory challenges and proposed paths forward. Cell Stem Cell. 2018;23(5):649–52.
9. Han MM, et al. Nanoengineered mesenchymal stem cell therapy for pulmonary fibrosis in young and aged mice. Sci Adv. 2023;9(29):eadg5358.
10. Richeldi L et al. Nerandomilast in patients with idiopathic pulmonary fibrosis. N Engl J Med, 2025.
11. Kolb M, Crestani B, Maher TM. Phosphodiesterase 4B inhibition: a potential novel strategy for treating pulmonary fibrosis. Eur Respir Rev, 2023. 32(167).
12. Nakamura Y, Niho S, Shimizu Y. Cell-Based therapy for fibrosing interstitial lung Diseases, current Status, and potential applications of iPSC-Derived cells. Cells. 2024;13(11):893.
13. Alvarez-Palomo B, et al. Induced pluripotent stem cell-derived lung alveolar epithelial type II cells reduce damage in bleomycin-induced lung fibrosis. Stem Cell Res Ther. 2020;11(1):213.

Publisher's note