American Journal of Clinical and Experimental Medicine
2025, Vol. 13, No. 4, pp. 99-134
https://doi.org/10.11648/j.ajcem.20251304.15

Research Article

Regenerative Therapies in the Treatment of Idiopathic Pulmonary Fibrosis: A Literature Review

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Abstract

Idiopathic Pulmonary Fibrosis (IPF) is a disease that leads to respiratory failure and subsequent death. To prevent chronic lung diseases from rising further up the list of leading causes of death worldwide, new innovative therapeutic approaches are needed. This work aims to present a literature review on advances in regenerative therapies in the treatment of IPF. The bibliographic strategy of this research used papers published in last ten years taken from the electronic databases PubMed and Capes Periodical Portal, which include the current understanding of this pathology, and the different treatment modalities. The majority of selected articles were concentrated in the last three years of this review, corroborating the expectation of recent advancements given the current massive scientific research on IPF. This review focused on current treatments, their limitations and investigated cutting-edge research in regenerative therapies. The research resulted in the presentation of ongoing studies and therapies segregated between pharmacological manipulation and the use of stem cells. Both categories of treatment focus on restoring endogenous lung repair or targeting pathways that inhibit dysregulated regeneration. Genetic and epigenetic factors were constantly highlighted as extremely necessary for the diagnosis. Conclusively, given the heterogeneity of this pathology, the authors propose, for the next general IPF treatment protocol, the inclusion of a combination of therapies, accentuating the pro and post-installed disease components. Encouraging the established of specialized health centers is also part of the findings of this research. They promote close cooperation between pulmonologists, radiologists, biomedical geneticists, pathologists, among others.

Keywords

Idiopathic Pulmonary Fibrosis, Therapeutic Approach, Regenerative Therapies

1. Introduction

Idiopathic Pulmonary Fibrosis (IPF) is a chronic, progressive, and devastating interstitial lung disease, restricted to the lungs, with no clearly known etiological cause, receiving the name Idiopathic [17]. It mainly affects adult patients, over 50 years old and in a proportion of 2-3 men to 1 woman [3]. In Brazil, Baddini-Martinez and Pereira estimated, based on data from the USA, an annual incidence of 3.5-5.1/100,000 inhabitants and a prevalence of 7.1-9.4/100,000 inhabitants [5]. Mortality is high, and most patients have an estimated survival of 3-5 years without treatment.

Possible factors causing pulmonary fibrosis include smoking, exposure to environmental impurities, occupational risks such as asbestos dust or silica, inhalation of toxic gases,

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Received: 3 July 2025; **Accepted:** 24 July 2025; **Published:** 18 August 2025

certain medications, autoimmune diseases, genetic factors, aging, and idiopathic causes. Other risk factors and related complications include pulmonary emphysema, gastroesophageal reflux disease, obstructive sleep apnea, and chronic viral infections [3].

IPF occurs due to the thickening and scarring of lung tissues, leading to impaired lung function or insufficient breathing. This disease involves the generation of scar tissue in the lungs, which dominates the thickening and stiffening of the lung walls, resulting in a loss of flexibility, making it difficult to supply oxygen to the bloodstream effectively.

The most common signs and symptoms of IPF are persistent dry cough and progressive dyspnea on exertion. Lung crackles and clubbing may also be present. The diagnosis is made by excluding some diseases and may begin with checking different symptoms and conducting some tests to reach a final diagnosis. Among the tests, high-resolution computed tomography, surgical lung biopsy or both stand out [19].

Among the current treatments to help control the progression of the disease, and provide comfort for the patient, are corticosteroids, immunosuppressants, oxygen therapy, lung transplantation and antifibrotic medications. Antifibrotics, including Nintedanib and Pirfenidone, aim to reduce inflammation and slow healing in the lungs. Although they do not cure, they can help prolong life, but they have side effects [26].

IPF treatment is constantly evolving. Future perspectives in the management of IPF are focused on the development of more effective therapies that aim not only to slow the progression of the disease, but to reverse pulmonary fibrosis. Challenges for this treatment include early diagnosis, disease heterogeneity and lack of curative treatments [34].

Regenerative medicine works to restore and repair tissues, organs, and functions of the human body. It seeks to develop therapies and approaches to replace or regenerate damaged cells, tissues, and organs. The main objective is to restore the body's normal function. In this sense, stem cells play a crucial role [1].

In addition to stem cells, other regenerative medicine approaches include the use of biomaterials, nano therapy, gene therapy, cell therapy, and tissue engineering [37].

Numerous research studies link susceptibility to IPF to various genetic and epigenetic factors and potential contributions of variants and interactions [37, 26, 22]. Although the real etiology of IPF is not completely known, there is evidence that it is inherited in an autosomal dominant manner with variable penetrance and represents 2% to 20% of all cases of idiopathic interstitial pneumonia [32].

Aging is an important risk factor in the disease, with mitochondria being prominent in its onset and progression. There are currently therapeutic approaches focused on improving mitochondrial dysfunction [10].

According to statistics from the Synapse database, there are a total of 341 research and development pipelines worldwide in the direction of this disease, with 4 drugs approved on the market, 6 projects in phase III clinical trials, 40 projects in phase II clinical trials and 45 projects in phase I clinical trials [39].

The future of IPF treatment is seen through innovations in the integration of early and less invasive diagnosis, with biomarkers acting as important pieces, as well as research into therapies aimed at more than restricting the progression of the disease, but reversing fibrosis and, therefore, promoting the restitution of natural tissue [3].

This project is justified by the need to reverse the IPF process. Being a disease that is difficult to treat and has a dismal prognosis, a survey of the literature on it contributes to organizing current knowledge and developing possible new treatment strategies. It also contributes to a better understanding of the reasons that can lead to fibrosis, which can affect several organs, as well as the anticipation of this propensity through research into the value of potential early biomarkers. Considering the current scenario, due to the grim prognosis and lack of cure for IPF, the importance of addressing studies that can support actions for treatment and possible cure of the disease is evident.

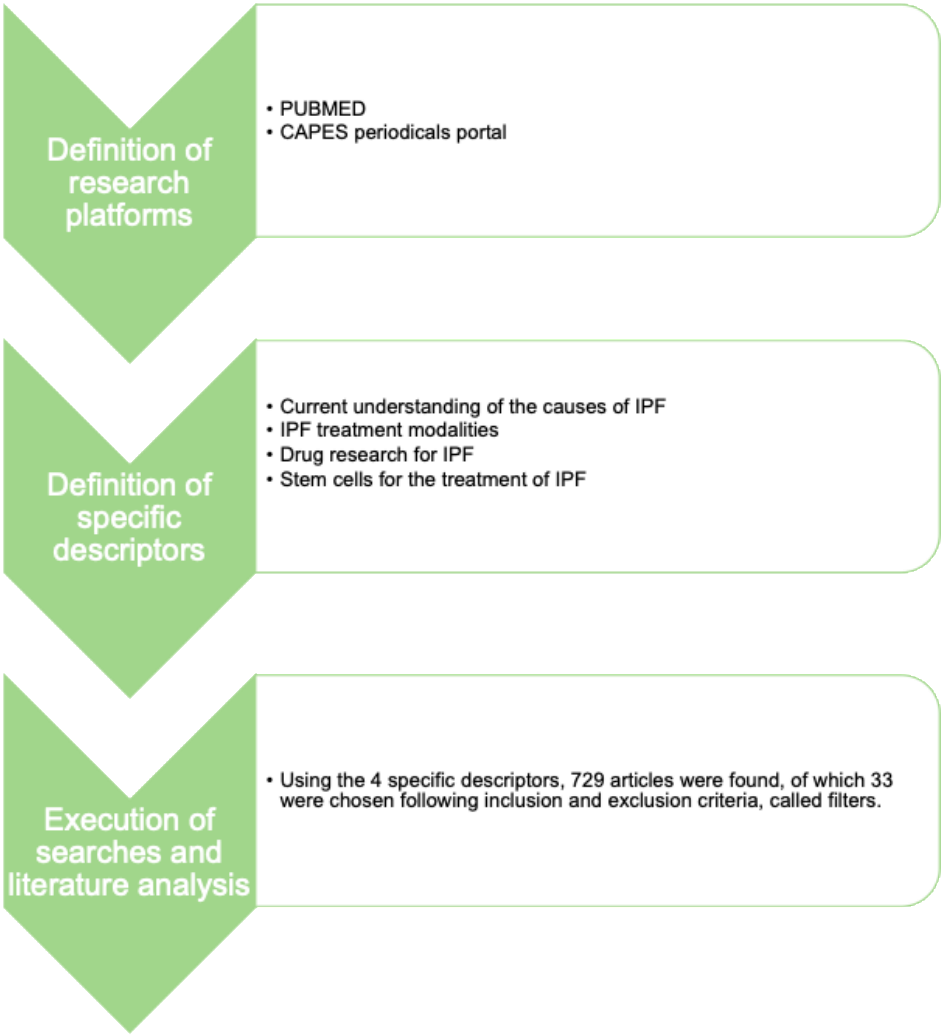
This work has the general objective of conducting a literature review on advances in the treatment of IPF. This review was conducted in order to seek information about potential etiologies of this disease, research current treatments and their limitations, investigate cutting-edge research in regenerative therapies, culminate in a discussion of the differences between current treatments and regenerative therapies, and to point out potential paths forward.

2. Methodology

The study involved a systematic and integrative bibliographic review using literature between January 2014 and December 2024. It comprised original scientific articles, published in scientific journals. All written in Portuguese, English, or Spanish.

Exclusion criteria were theses, monographs and dissertations, materials from non-scientific journals, articles not peer-reviewed and written in languages other than Portuguese, English or Spanish, topics outside the scope of this work and outside the chosen period.

The configuration of the results was obtained by executing three sequential steps, exemplified in Figure 1 and Figure 2. In step number 1, the research platforms were established (PubMed and Capes newspaper portal). The second step included the research terms, called determined specific descriptors, which were: Current understanding of the causes of IPF; IPF treatment modalities; Drug Research for IPF; Stem cells for the treatment of IPF. The third and final step consisted of carrying out searches and analyzing the literature.



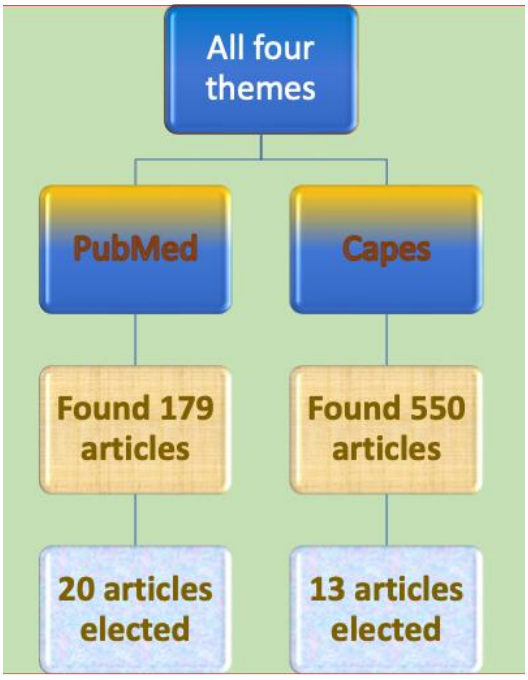


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Figure 1. *Flowchart demonstrating the research steps and the result.*

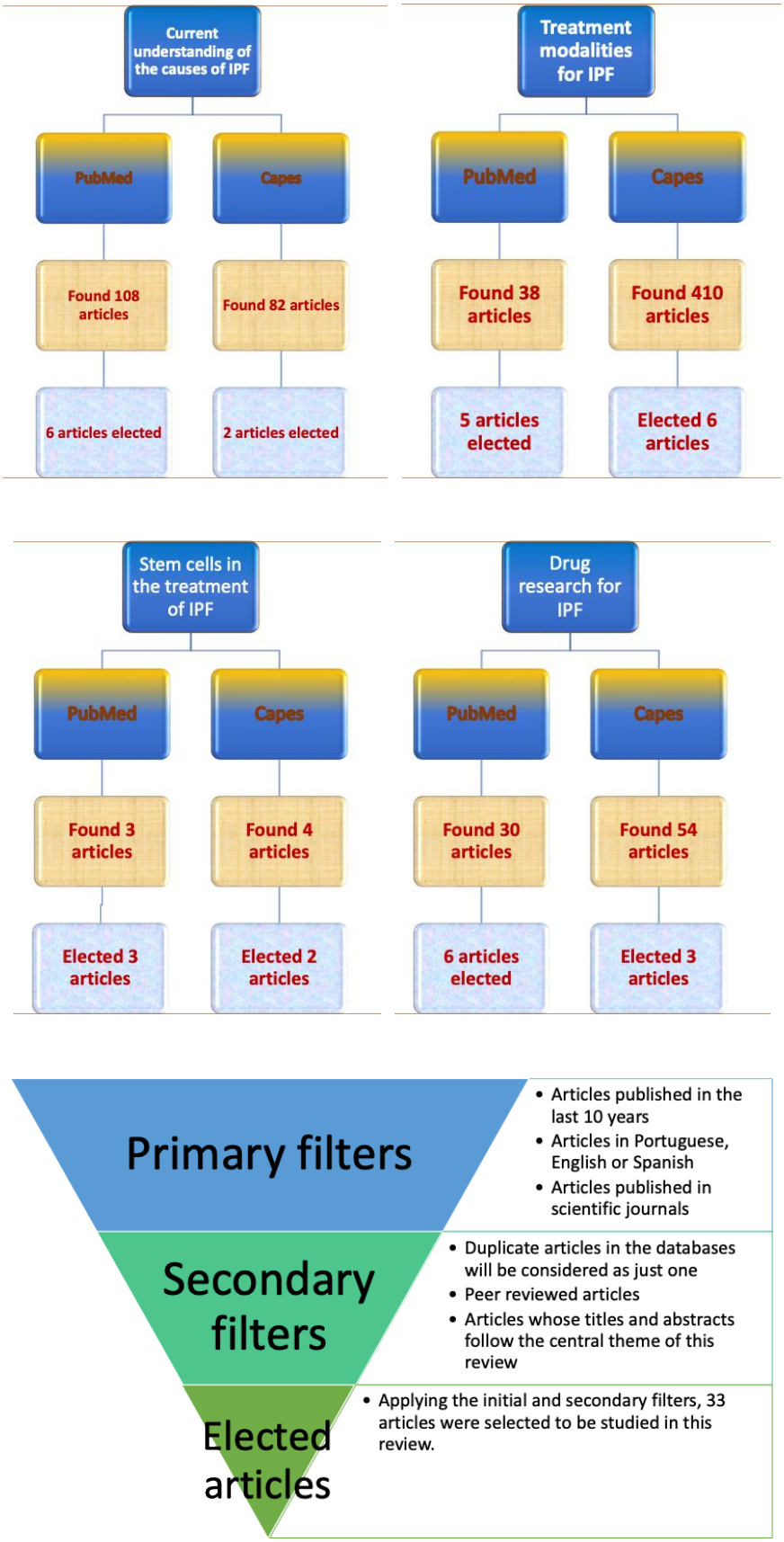

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Figure 2. *Flowchart demonstrating the research steps for the four specific descriptors in the electronic databases, as well as the inclusion and exclusion criteria called filters.*

In the end, 729 titles were found, and 33 articles were then chosen to be studied in this review. Articles that appeared as duplicates in the databases were excluded and only one copy was left.

This article is exempt from submission to the Research Ethics Committee (REC) because it is an integrative literature review, therefore it does not involve research on human beings.

3. Results and Discussion

Following the steps presented in the methodology, 33 articles were studied (shown in Table 1) and categorized by title, year of publication, country of publication, authors, general objective and result.

Table 1. *Summary of articles studied.*

	TITLE	YEAR	COUNTRY	AUTHORS	OBJECTIVE	RESULTS
1	Idiopathic Pulmonary Fibrosis: Review of Current Knowledge	2024	Slovakia	Muri, et al.	Presentation of ongoing stem cell trials	Mesenchymal stem cells have shown promising results; Research is underway for new options such as PRM-151, Pamrevlumab and Galectin-3
2	Pulmonary fibrosis: Is stem cell therapy the way forward?	2023	Pakistan	Ikrama, et al.	Importance of stem cells in the treatment of IPF	Stem cells: regeneration and reduction of inflammation; Challenges: costs, ethical issues and immunological compatibility.
3	Stem cell-based therapy for pulmonary fibrosis	2022	China	Wenzhao Cheng, Yiming Zeng, Dachun Wang	Combination of stem cell therapies and gene therapy	Lung transplant: The only option for terminal stages; Stem cells: therapy for lung regeneration;
4	Therapeutic Applications of Mesenchymal Stem Cells in Idiopathic Pulmonary Fibrosis	2021	China	Yang, et al.	Presentation of ongoing stem cell trials	Mesenchymal stem cell (MSC) therapy regulates immunity and promotes tissue repair
5	Mesenchymal stem cells and pulmonary fibrosis: a bibliometric and visualization analysis of literature published between 2002 and 2021	2023	China	Yang, et al.	Presentation of ongoing stem cell trials	Analysis of 1,457 publications on mesenchymal stem cells (MSCs) in the treatment of (IPF), increase in research in the area; USA led publications
6	Molecular Mechanisms of Pulmonary Fibrogenesis and Its Progression to Lung Cancer: A Review	2019	Japan	Tomonari Kinoshita, Taichiro Goto	Oncogenic panorama of IPF	Common molecular mechanisms between IPF and lung cancer;
7	The oncogenic landscape of the idiopathic pulmonary fibrosis: a narrative review	2022	Italy	Stella, et al.	Oncogenic panorama of IPF	Similarities of the molecular mechanisms of IPF with cancer; distinct dynamics; Personalized strategies.
8	Turning the tide: From fibrosis to regeneration following anti-fibrogenic cell vaccination	2022	United States of America	Ira Phadke, Alka Dwivedi, Naomi Taylor	Oncogenic panorama of IPF	Proposal for an immunotherapeutic vaccine targeting specific antigens of fibrogenic cells, such as ADAM12 in the liver and GLI1 in the lungs. Potential treatment for fibrotic diseases.

	TITLE	YEAR	COUNTRY	AUTHORS	OBJECTIVE	RESULTS
9	Lysophophatidic acid receptor 1 inhibition: a potential treatment target for pulmonary fibrosis	2024	United States of America	Volkmann et al.	Potential treatments	Investigation of ATX and LPAR1 Inhibitors as Promising Therapies in Clinical Trials for the Treatment of the Disease
10	Targeting Alveolar Repair in Idiopathic Pulmonary Fibrosis	2021	United Kingdom	Ptasinski VA, Stegmayr J, Belvisi MG, Wagner DE, Murray LA.	Potential treatments	Stem cell modulation; anti-inflammatory and antifibrotic therapies; the body's own repair capacity; promotion of tissue regeneration without stimulating the formation of pathological scars; understanding the molecular mechanisms that regulate alveolar repair; identification of therapeutic targets improving the prognosis of patients with IPF.
11	Target tumour suppressor p53 for organ fibrosis therapy	2024	China	Bao, et al.	Potential treatments	Modifying p53 activity is a promising therapeutic approach to treat IPF
12	Idiopathic pulmonary fibrosis and the role of genetics in the era of precision medicine	2023	Spain	Gonzalez, et al.	Genetic sequencing (protocol)	Explores how rare and common genetic variants influence the risk and progression of idiopathic pulmonary fibrosis (IPF). It also discusses how genomic technologies can improve diagnosis, prognosis, and genetic screening strategies for IPF.
13	The Inflammasome NLR Family Pyrin Domain-Containing Protein 3 (NLRP3) as a Novel Therapeutic Target for Idiopathic Pulmonary Fibrosis	2022	United States of America	Biancatell, et al.	Potential treatments	Reviews evidence on NLRP3 activation in idiopathic pulmonary fibrosis and highlights recent advances in direct and indirect NLRP3 inhibitors.
14	The Genetic and Epigenetic Footprint in Idiopathic Pulmonary Fibrosis and Familial Pulmonary Fibrosis: A state-of-the-Art Review	2022	Italy	Tirelli, et al.	Epigenetic factors of IPF such as biomarkers or druggable targets	Analyzes the genetic and epigenetic mechanisms involved in idiopathic pulmonary fibrosis (IPF) and familial pulmonary fibrosis (FPF). Highlights mutations in genes related to telomerase (TERT, TERC, PARN, RTEL1) and surfactant proteins (SFTPC, SFTPA1, SFTPA2, ABCA3) as well as polymorphism in the MUC5B and TOLLIP genes, which contribute to fibrogenesis. The study also addresses epigenetic alterations such as DNA methylation.
15	European Respiratory Society statement on familial pulmonary fibrosis	2022	France	Borie, et al.	Genetic sequencing (protocol)	Addresses genetic predisposition in IPF evidenced by several genetic mutations associated with the disease. The statement provides guidelines on genetic sequencing, clinical counseling, management and screening of patients with familial pulmonary fibrosis (FPF) and their family members, aiming

	TITLE	YEAR	COUNTRY	AUTHORS	OBJECTIVE	RESULTS
						to improve the diagnosis and treatment of this condition.
16	Genetic Risk Factors for Idiopathic Pulmonary Fibrosis: Insights into Immunopathogenesis	2020	United States of America	Jacob E Michalski, David A Schwartz	Genetic factors involved in IPF	It explores the genetic factors associated with the development of IPF and their implications in the immunopathogenesis of the disease. The authors highlight that genetic variations account for at least one third of the risk of developing IPF. Among these, the gain-of-function variant in the promoter of the MUC5B gene is indicated as the most significant risk factor, genetic or otherwise, for the disease.
17	Revealing the Pathogenic and Aging-related Mechanisms of the Enigmatic Idiopathic Pulmonary Fibrosis	2014	Mexico	Moisés Selman, Annie Pardo	Genetic variants in the aged lung	Explores the pathogenetic and age-related mechanisms of idiopathic pulmonary fibrosis (IPF). The authors propose that aberrant activation of alveolar epithelial cells and fibroblasts in aged lungs plays a crucial role in the pathogenesis of IPF
18	Precision medicine advances in idiopathic pulmonary fibrosis	2023	United States of America	Karampitsakos, et al.	Precision medicine in IPF patients	The work emphasizes that the adoption of precision medicine strategies in IPF has the potential to transform disease management but requires continued effort to integrate these scientific discoveries into daily clinical practice.
19	Molecular and Genetic Biomarkers in Idiopathic Pulmonary Fibrosis: Where Are We Now?	2023	Greck	Tomos, et al.	Epigenetic factors of IPF such as biomarkers or druggable targets	The article highlights the relevance of molecular and genetic biomarkers in understanding and managing IPF, emphasizing the need for further research to validate and implement these biomarkers in clinical practice.
20	Research progress in the molecular mechanisms, therapeutic targets, ad drugs development of Idiopathic Pulmonary Fibrosis	2022	China	Ma, et al	Genetic factors involved in IPF	This article summarizes advances in understanding the molecular mechanisms of IPF and how these discoveries are being translated into new therapeutic strategies and drug development aimed at improving management and clinical outcomes for patients.
21	Pharmacological expansion of type 2 alveolar epithelial cells promotes regenerative lower air repair	2024	United States of America	Shao, et al.	Potential treatments	This article suggests that DPP4 inhibition may be a promising strategy to stimulate lung regeneration in diseases such as idiopathic pulmonary fibrosis (IPF) offers a new therapeutic approach for degenerative lung conditions.
22	US patent covers brilaroxazine in treating IPF, like diseases	2024	United States of America	Bhat; Laxminarayan	Potential treatments	In 2024, the United States Patent and Trademark Office (USPTO) granted patent No. 12053477 to Reviva Pharmaceuticals Holdings

	TITLE	YEAR	COUNTRY	AUTHORS	OBJECTIVE	RESULTS
						for the use of brilaroxazine in the treatment of idiopathic pulmonary fibrosis (IPF) and other fibrosing lung diseases, including those associated with chronic obstructive pulmonary disease (COPD), sickle cell anemia, scleroderma, and lung cancer.
23	Idiopathic Pulmonary Fibrosis: Addressing the current and future therapeutic advances along with the role of Sotatercept in the management of pulmonary hypertension	2023	India	Hadi, et al.	Potential treatments	The article provides valuable insights into current and future therapeutic options for IPF, emphasizing the need for continued research to improve patient outcomes.
24	Promising advances in treatments for the management of idiopathic pulmonary fibrosis	2024	Italy	Carmelo Sofia, Alessia Comes, Giacomo Sgalla, Luca Richeldi	Potential treatments	This multifaceted approach is expected to significantly improve the overall treatment of patients with IPF, supporting optimistic expectations of reversing fibrotic changes and ultimately restoring lung function to a normal state.
25	A small-molecule TNIK inhibitor targets fibrosis in preclinical and clinical models	2024	China	Feng Ren, et al.	Epigenetic factors of IPF such as biomarkers or druggable targets	A generative AI platform was used to unbiasedly identify TNIK as an antifibrotic target. TNIK has also been implicated in multiple hallmarks of aging, suggesting broader therapeutic potential
26	Exploring Therapeutic targets for molecular therapy of idiopathic pulmonary fibrosis	2024	China	Li, et al.	Genetic factors involved in IPF	It has mainly focused on therapeutic targets that have not only entered clinical trials but have also been publicly published with their clinical results. Until now, many researchers have focused on the downstream effectors of gene expression, such as cytokines and enzymes. Epigenetic modification also plays a vital role in IPF.
27	Current and Novel Treatment Modalities of Idiopathic Pulmonary Fibrosis	2024	United States of America	Mahnoor Arshad, Zoraize Moeez Athar, Tasneem Hiba	Current treatment modalities	This article provides an overview of current treatment modalities for IPF and explores the need for new therapeutic approaches.
28	The Bright side of fibroblastic: molecular signature and regenerative cues in major organs	2021	Portugal	Rita N Gomes, Filipa Manuel, Diana S Nascimento	Potential treatments	The positive side of fibroblasts: molecular signature and regenerative signals in major organs
29	Human Adipose-derived Mesenchymal Stem Cells Attenuate Early Stage of Bleomycin Induced Pulmonary Fibrosis: Comparison	2016	India	Reddy, et al.	Presentation of ongoing stem cell trials	In the present study, AD-MSCs were shown to be effective in improving the symptoms of pulmonary fibrosis, increasing survival capacity and protecting against pulmonary fibrosis comparatively better than

	TITLE	YEAR	COUNTRY	AUTHORS	OBJECTIVE	RESULTS
	with Pirfenidone					pirfenidone.
30	Engineered Lung Tissues Prepared from Decellularized lung slices	2022	United States of America	Leiby, et al.	Precision medicine in IPF patients	In summary, this protocol describes a robust system to generate engineered lung tissues for culture studies of AEC2s, fibroblasts, and endothelial cells within acellular ECM lung slice scaffolds.
31	Early decrease in erector spinae muscle area and future risk of mortality in idiopathic pulmonary fibrosis	2020	Japan	Nakano, et al.	Epigenetic factors of IPF such as biomarkers or druggable targets	Early decrease in ESMCSA may be a useful predictor of prognosis in patients with IPF.
32	Innovative Pre-Clinical Data Using Peptides to Intervene in the Evolution of Pulmonary Fibrosis	2023	Brazil	Simon, et al.	Potential treatments	This work aimed to apply a therapeutic alternative using immunomodulatory peptides in a murine model of chronic pulmonary fibrosis.
33	Administration of Collagen Peptide Prevents the Progression of Pulmonary Fibrosis in Bleomycin-Treated Mice	2023	Japan	Yoshihara, et al.	Potential treatments	The results of this study suggest that CP (PEPTIDE COLLAGEN) supplementation prevents the development of IPF by acting as an anti-inflammatory agent.

Source: Authors

The research included a Brazilian reference, the others being foreign, of which the United States and China led, with nine and seven references respectively. These were followed by Italy and Japan with three, India with two, and Mexico, Spain, Slovakia, France, Greece, Portugal, England and Pakistan, with one reference each, as shown in Figure 3.

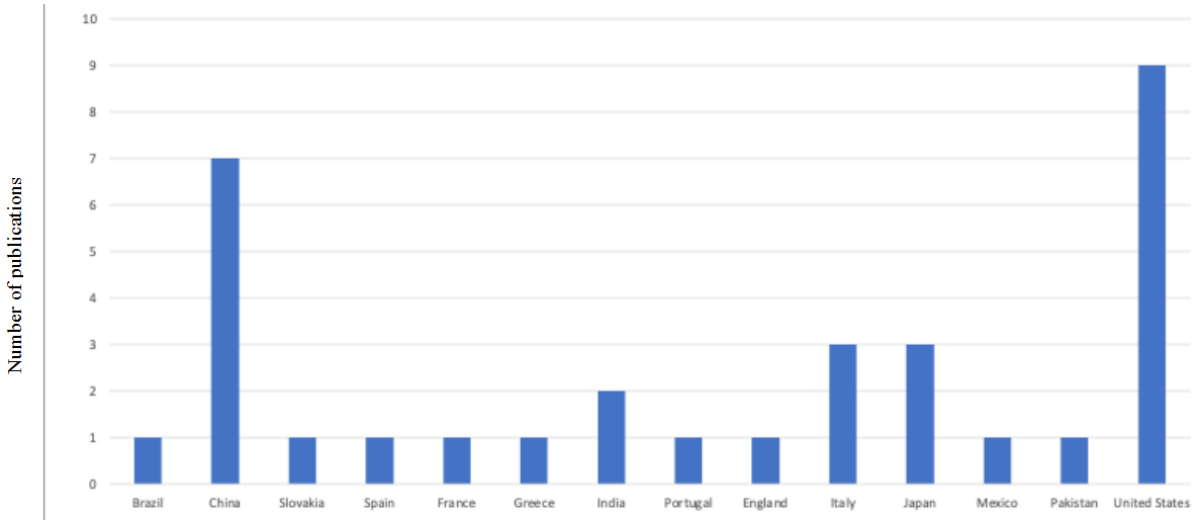

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Figure 3. *Bibliometric analysis of countries and number of publications used.*

The period of this review covers 2014 to 2024. It is noted that only one article per year was selected for 2014, 2016 and 2019. No articles were included for 2015, 2017 and 2018. In 2020, two articles were considered and three articles in 2021. In the last three years considered in this review, most of the articles selected can be seen corroborating the expectation of this research regarding a massive increase in scientific investigation into Idiopathic Pulmonary Fibrosis. Eight articles were considered from 2022, eight in 2023 and nine from 2024 (Figure 4).

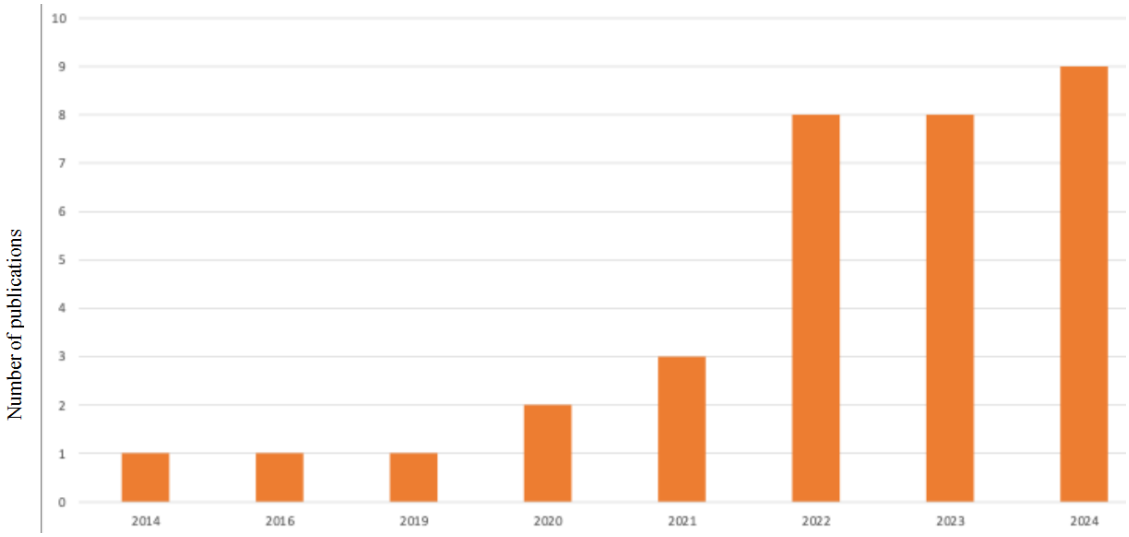

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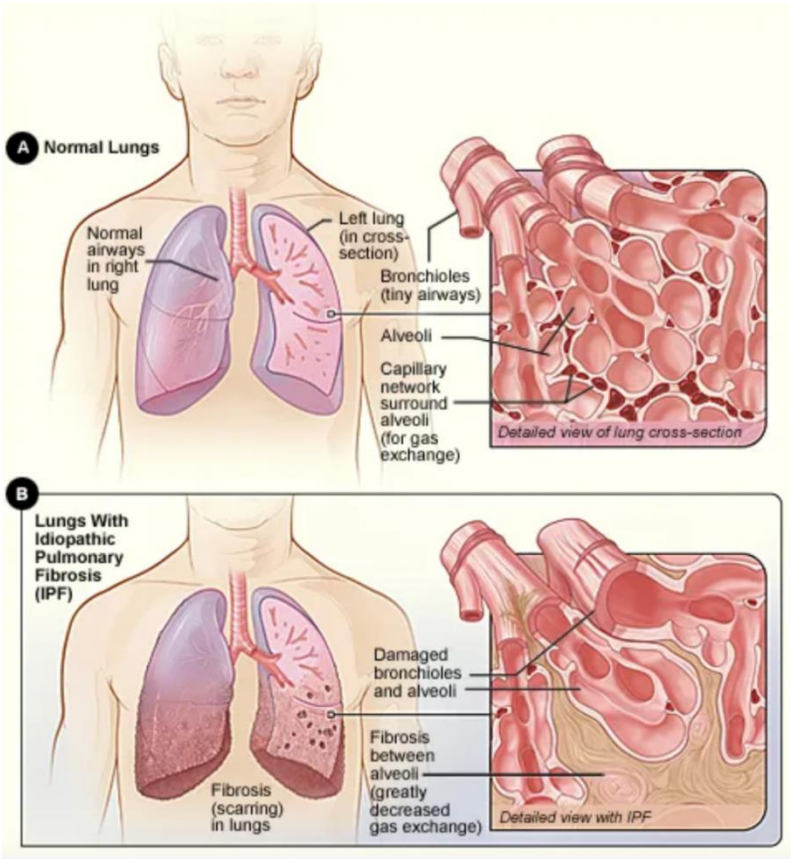
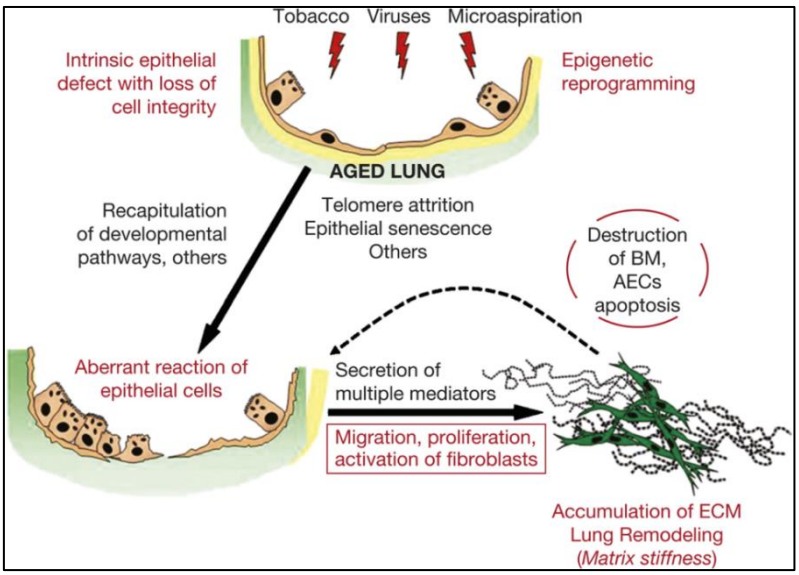
Figure 4. *Bibliometric analysis of the year and number of publications used.*



Source: Synapse (2024)

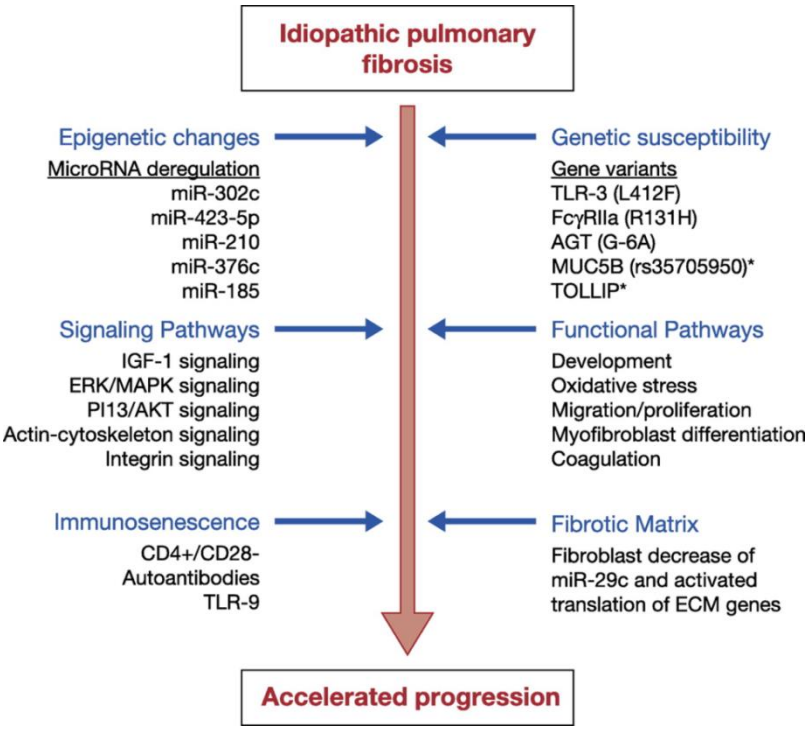
Figure 5. *Comparison between a healthy lung (A) and a diseased lung (B).*

The less current literature (2014 - 2019) covers a range of information about the pathology of IPF. Figure 5 shows a comparison between a healthy lung and a diseased lung [39]. The references from this period deal mainly with symptoms, diagnosis, complications of the disease, incidences and present the understanding of the scientific community that the aberrant activation of alveolar epithelial cells and fibroblasts plays a critical role in the pathogenesis of IPF. Figure 6 proposes the integral model involved in the pathogenesis of IPF [31].



Source: Selman, Prado (2014)

Figure 6. *Integral model involved in the pathogenesis of IPF.*



Source: Selman, Prado (2014)

Figure 7. *Mechanisms associated with the acceleration rate of IPF.*

The susceptibility of the disease in the aged lung is also addressed, with characteristics of aging, for example, genomic instability, telomere wear, epigenetic changes, mitochondrial dysfunction and cellular senescence [6]. These characteristics have been proposed as essential mechanisms for the development of IPF. Figure 7 presents the mechanisms associated with the IPF acceleration rate [31]. Therefore, the relevance of proposing clinical genetic tests for prognosis, predisposition, and even reliable biomarkers, which are defined as entities that can be measured experimentally and indicate the occurrence of a certain normal or pathological function of an organism or a response to a pharmacological agent, can already be seen in this period.

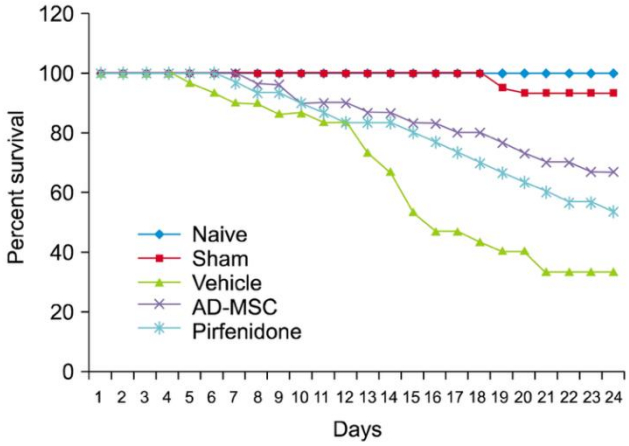
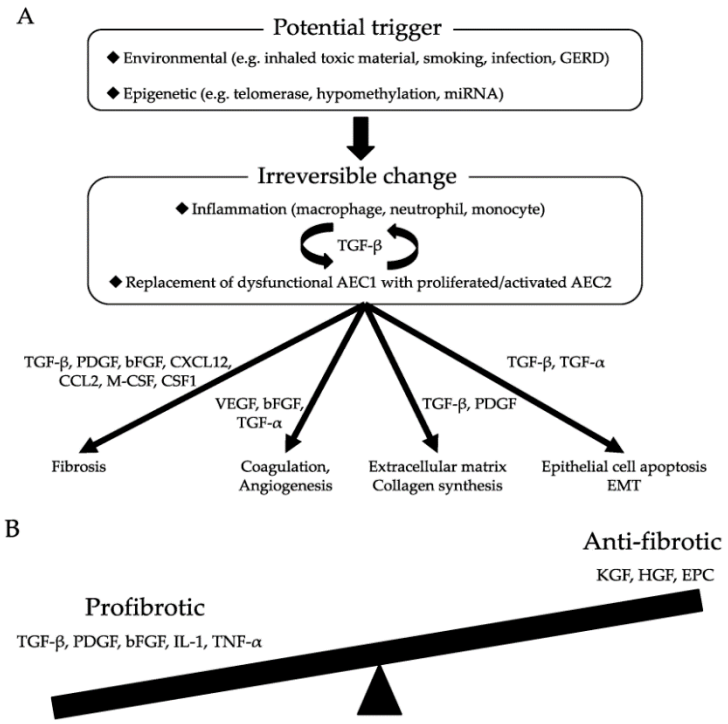


Figure 8. *Survival estimates for animals with bleomycin-induced pulmonary fibrosis.*

Control cases are: Na ïve, Sham and Vehicle
Source: Reddy, et al. (2016)



Source: Kinoshita, Goto (2019)

Figure 9. *(A) Molecular mechanisms of pulmonary fibrosis; (B) Imbalance of pro-fibrotic and anti-fibrotic mediators leads to defective regeneration and aberrant remodeling, resulting in the pathological transformation of pulmonary fibrosis.*

Another article from this period presents a preliminary comparison between treatment therapy using stem cells versus the current treatment using the antifibrotic Pirfenidone, showing the superiority of regenerative therapy. Figure 8 presents this comparison using survival estimates for animals with bleomycin-induced pulmonary fibrosis [29].

A large majority of preclinical and clinical investigations for IPF therapies in the past have focused on either a "pathological myofibroblast behavior inhibition" approach or an anti-inflammatory approach. The two currently approved therapies have been classified as falling under the former approach. The latter approach, e.g., triple treatment with N-acetylcysteine, prednisone, and azathioprine, has not been an effective treatment strategy for IPF, as reported by vast majority of clinical trials.

Still in the group of less current articles, the oncological panorama of IPF was explored. It is clear that tumorigenesis and pulmonary fibrosis exhibit highly heterogeneous behaviors, warranting personalized therapeutic approaches. However, optimal management of patients with IPF and/or lung cancer requires understanding the pathogenic mechanisms and molecular pathways common to both diseases. Figure 9 presents the molecular mechanisms of IPF. Table 2 displays the main factors involved in both IPF and lung cancer [16].

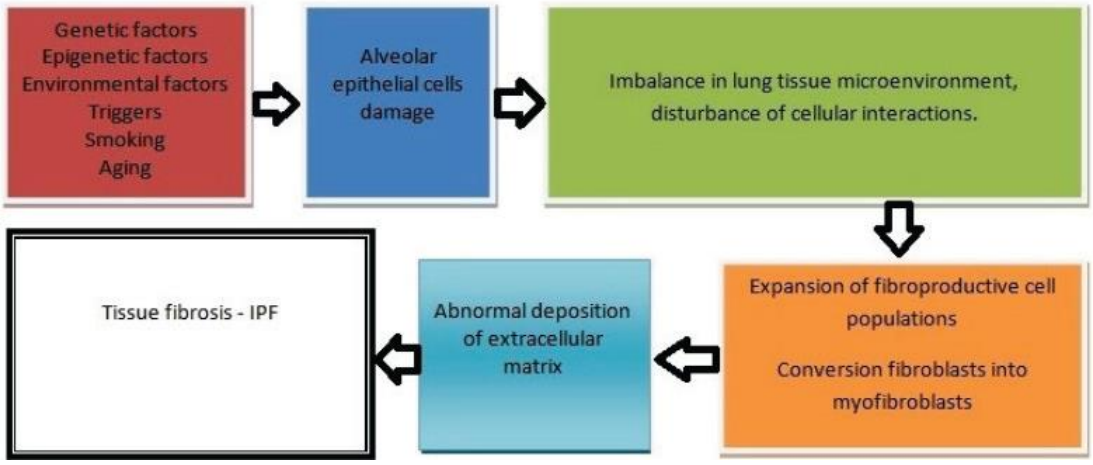
Table 2. *Main factors involved in both IPF and lung cancer.*

Mediators		IPF	Lung Cancer
Abnormal mRNA	let-7	down-regulated	down-regulated
	miR-21	up-regulated	up-regulated
	miR-29	down-regulated	down-regulated
	miR-30	down-regulated	down-regulated
	miR-155	up-regulated	up-regulated
	miR-200	down-regulated	down-regulated
Cell-free DNA	-	up-regulated	up-regulated
Glycoprotein	Thy-1	down-regulated	down-regulated
Connexin	Cx43	down-regulated	down-regulated
Growth Factors	TGF-β	up-regulated	up-regulated
	PDGF	up-regulated	up-regulated
	VEGF	up-regulated	up-regulated
Migration	FGF	up-regulated	up-regulated
	laminin	up-regulated	up-regulated
	fascin	up-regulated	up-regulated
	heat shock protein 27	up-regulated	up-regulated
Pathways	Wnt pathway	up-regulated	up-regulated
	PI3K/Akt pathway	up-regulated	up-regulated
	FAM	up-regulated	up-regulated
Immune Cells	MDSC	up-regulated	up-regulated
	Treg	down-regulated	up-regulated

Source: Kinoshita, Goto (2019)

The most current articles (2020 - 2024) present, in addition to the characterization of the disease, the frequent search for a regenerative therapy approach, based on the current understanding of IPF as a disease caused by environmental injuries in a genetically susceptible lung, thus accentuating the role of clinical genetic testing. Figure 10 presents a diagram of the pathogenesis of IPF [24]. In Figure 11, the pathological process of IPF is presented, [21] in Figure 12, the

histological pattern compatible with IPF, and in Figure 13, a high-resolution computed tomography representation is shown, which is a fundamental imaging test in the IPF diagnostic algorithm [24].



Source: Muri, et al. (2024)

Figure 10. *Pathogenesis of IPF.*

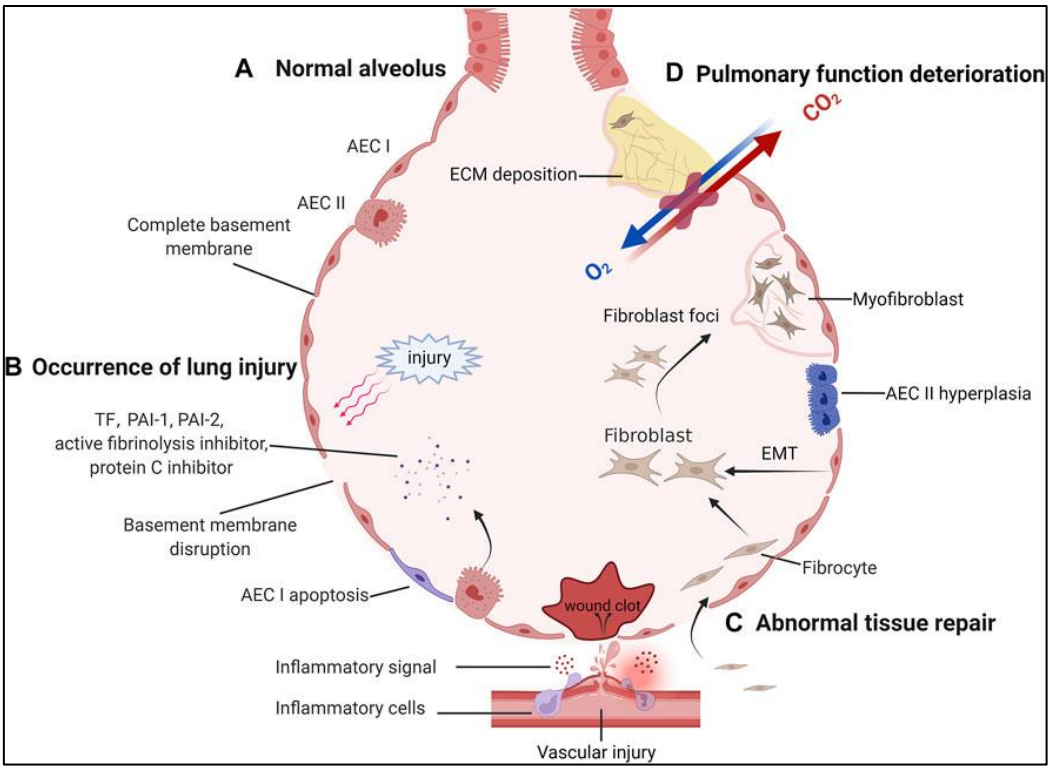


Figure 11. *Pathological process of IPF.*

A) After normal alveoli are damaged and repaired abnormally, irreversible deterioration of lung function occurs. The normal alveolus has a complete basement membrane and gas exchange function. (B) When the continuity of the basement membrane is disrupted by external injury, damaged capillaries, and activated AECs release inflammatory signals and clotting factors, forming a local inflammatory microenvironment. (C) If damage persists, abnormal repair is initiated. Lung mesenchymal progenitors, fibrocytes recruited to the lung, and endothelial cells undergoing EMT may aggregate to form fibroblast foci and differentiate into matrix-secreting myofibroblasts. To compensate for the local blood supply to the alveoli, new blood vessels are gradually formed. (D) As fibroblast foci increase, more ECM is deposited and cross-linked, triggering a deterioration in lung compliance and gas exchange function.
Source: Ma, et al (2022)

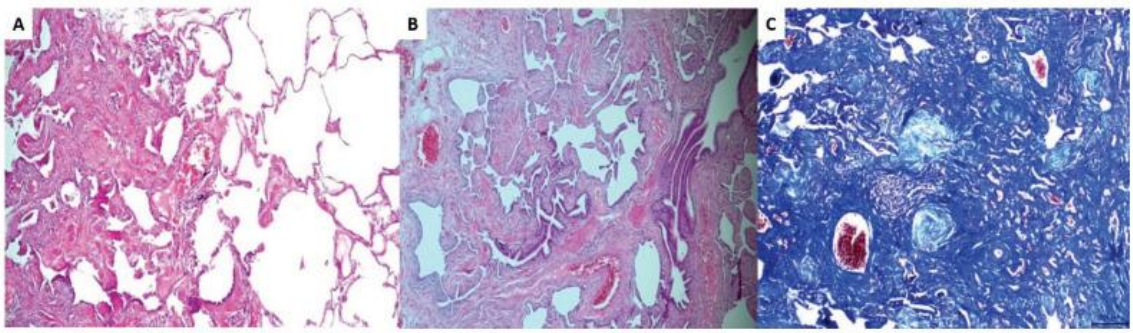


Figure 12. *Histological pattern compatible with IPF.*

Habitual interstitial pneumonia (hematoxylin-eosin (A, B) and Masson's trichrome (C), 50x) with evident heterogeneity in the distribution of pathological changes, in addition to areas of fibrosis at different levels of maturity and with multiple fibroblastic foci. Department of Histology and Embryology, Faculty of Medicine, University of Ostrava, Ostrava.
Source: Muri, et al. (2024)

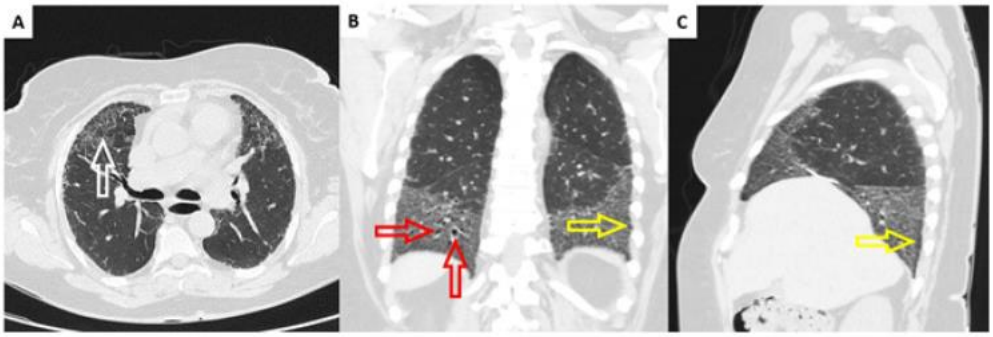
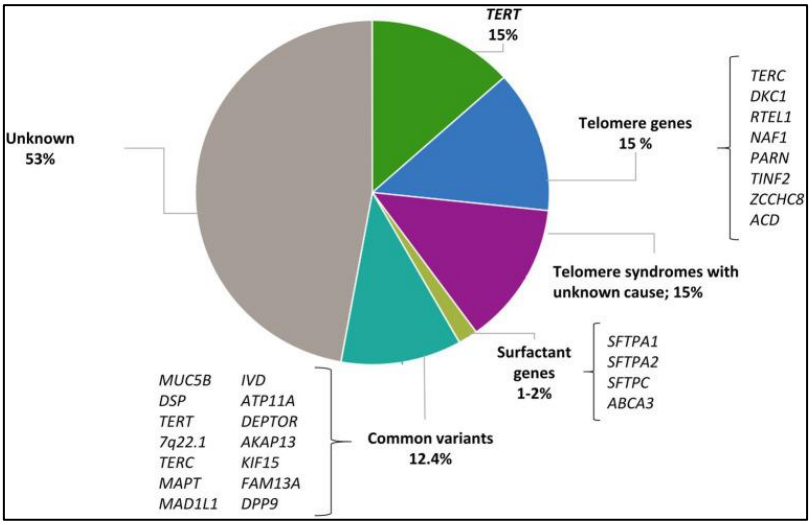


Figure 13. *Computed tomography of the lungs in a patient diagnosed with IPF.*

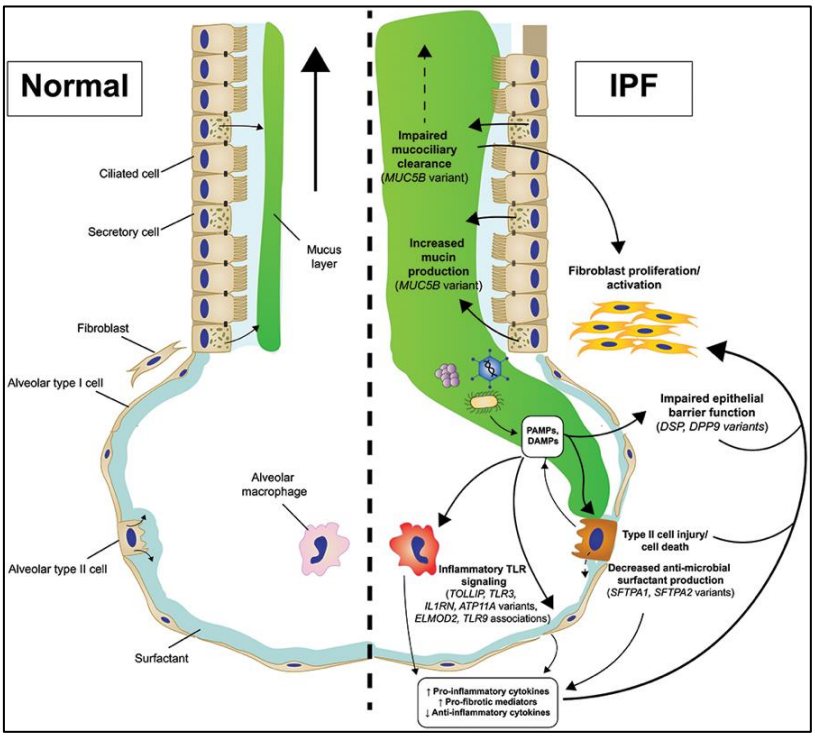
(A) HRCT scan of pulmonary fibrosis demonstrating reticular opacities (white arrow) and a predominant subpleural distribution. (B and C) demonstrate a predominant basal fibrotic change with traction bronchiectasis (red arrows) and honeycombing (yellow arrow). Department of Radiological Diagnostics, National Institute of Tuberculosis, Lung Diseases and Thoracic Surgery in Vyšné Hágy, Slovakia.
Source: Muri, et al. (2024)



Source: Gonzalez, et al (2023)

Figure 14. *Contribution of rare and common variants to IPF risk.*

Much of this literature emphasizes the genetic and epigenetic factors involved in IPF. Figure 14 presents a graph with the contribution of rare and common variants to the risk of IPF [2], Figure 15 presents the scheme of changes in innate immunity of genetic origin, contributed to the pathogenesis of IPF [23], and table 3 contains a summary of the main genes described in IPF and FPF (Familial Pulmonary Fibrosis) and their profibrotic mechanisms [40].



Source: Michalski, Schwartz (2020)

Figure 15. *Changes in innate immunity of genetic origin contributing to the pathogenesis of IPF.*

Table 3. *Summary of the main genes described in IPF and FPF and their profibrotic mechanisms.*

Gene [1]	Main Function	Profibrotic Mechanism
TERT	Telomerase	Decreased activity of telomerase
TERC	Reverse Transcription in Telomerase	Decreased activity of telomerase
PARN	Stability of mRNA in Telomerase	Shortening of telomeres
RTEL1	DNA helicase in Telomerase	Shortening of telomeres
SFTPA1	Modulate surface tension in the alveoli	Increased ER stress
SFTPA2	Modulate innate and adaptive immunity	Increased ER stress
SFTPC	Stabilize the surfactant fluid	Increased ER stress
ABCA3	Lipid transport across membranes	Increased ER stress and apoptosis
MUC5B	Mucin 5B production	Muco-ciliary disfunction
TOLLIP	Inhibitory adaptor protein within TLR	Decreased protection against ROS

1 TERT: telomerase reverse transcriptase; TERC: telomerase RNA component; PARN: poly(A)-specific RNase; RTEL1: telomere elongation regulator helicase-1; SFTPA1: surfactant protein A1; SFTPA2: surfactant protein A2; SFTPC: surfactant protein C; ABCA3: ATP-binding cassette subfamily A member 3; MUC5B: mucin 5B; TOLLIP: Toll-interacting protein; TLR: Toll-like receptors; ER: endoplasmic reticulum; ROS: reactive oxygen species.
Source: Tirelli, et al. (2022)

The current literature also presents the current treatment modalities and their limitations: These are diverse, from pharmacotherapy to lung transplantation, as summarized and presented in tables 4 and 5 [4, 14]. It is noted that both tables, extracted from different articles, agree with the majority of current modalities and their limitations.

Table 4. *Current treatment modalities for IPF.*

Treatment Modality	Description
Pirfenidone	Oral medication that reduces fibroblast activity and pro-inflammatory cytokines.
Nintedanibe	Oral medication that inhibits multiple tyrosine kinases involved in fibroblast proliferation.
Oxygen Therapy	It provides supplemental oxygen to improve oxygenation and relieve symptoms of hypoxemia.
Pulmonary Rehabilitation	Comprehensive programs, including exercise training, education, and support to improve lung function and overall well-being.
Lung Transplantation	Considered for patients with advanced idiopathic pulmonary fibrosis who meet specific criteria to improve survival and quality of life.

Source: Arshad, Athar, Hiba (2024)

Table 5. *Current treatment modalities for IPF with clinical effects and some therapies in development.*

Treatment	Mechanism of action	Clinical effects
Current therapies		
Pirfenidone	Antifibrotic and anti-inflammatory	Slows rate of decline in FVC
Nintedanibe	Antifibrotic and anti-inflammatory	Slows rate of decline in FVC
Oral corticosteroids, opioids	Antitussive	Decreases cough and improves quality of life
Anti-acids, proton pump inhibitors	Decreases GERD	Benefits unclear
Lung transplantation	Surgical replacement of one or both lungs	Available only as a potentially curative therapy
Therapies in development		
PRM-151	Recombinant human pentraxin-2; acts as an antifibrotic agent	Slows rate of decline in FVC
Pamrevlumab	Fully human recombinant monoclonal antibody to CTGF	Slows rate of decline in FVC
TD139	Small molecule inhibitor of galectin-3	Decreases plasma biomarkers of inflammation; study in progress to assess effect on FVC
PLN-74809	Blocks activation of the TGFβ pathway	Study in progress with end-points of safety, tolerability, and pharmacokinetics
TRK-250	Suppresses TGFβ expression	Study in progress to assess the safety and tolerability of single and multiple inhaled doses

Abbreviations: CTGF, connective tissue growth factor; FVC, forced vital capacity; GERD, gastroesophageal reflux disease; IPF, idiopathic PF.
Source: Ikrama, et al. (2023)

At present, only two antifibrotic drugs have been approved for use as appropriate pharmacotherapy for IPF. They are: Pirfenidone and Nintedanib. Pirfenidone has anti-inflammatory and antifibrotic action and acts on TNF-α and TGF-β receptors. Nintedanib blocks intracellular ATP binding points in specific tyrosine kinases and inhibits the action of receptors for FGF, PDGF and VEGF. Studies contemplating the use of Pirfenidone, such as CAPACITY

and ASCEND, as well as TOMORROW and IMPULSE, examining Nintedanib, demonstrate their help in improving patients' lives. Despite their beneficial effects, these medications are not curative and can only slow the progression of the disease, rather than preventing its progression altogether. Furthermore, they are associated with potential side effects and may not be suitable for all patients, highlighting the need for alternative treatment options.

An increasingly attractive prospect for emerging therapies for IPF is the pharmacological manipulation of pathways that restore endogenous lung repair or the targeting of pathways that inhibit dysregulated regeneration. The reparative properties of endogenous progenitor cells depend strongly on appropriate interactions with their environment, including interactions with the mesenchyme, extracellular matrix, and molecular signaling. Many of the signaling pathways normally implicated in lung development are also activated during and after lung injury, thus promoting tissue repair. Chronic aberrant activation of several of these pathways has, however, been associated with the development of chronic lung diseases. Although the scientific community currently has extensive knowledge about aberrantly activated signaling pathways and how they contribute to the pathogenesis of IPF, several of these pathways intersect and influence each other. This makes differential targeting of these pathways a significant challenge, and thus therapeutic combinations may be needed to overcome this obstacle.

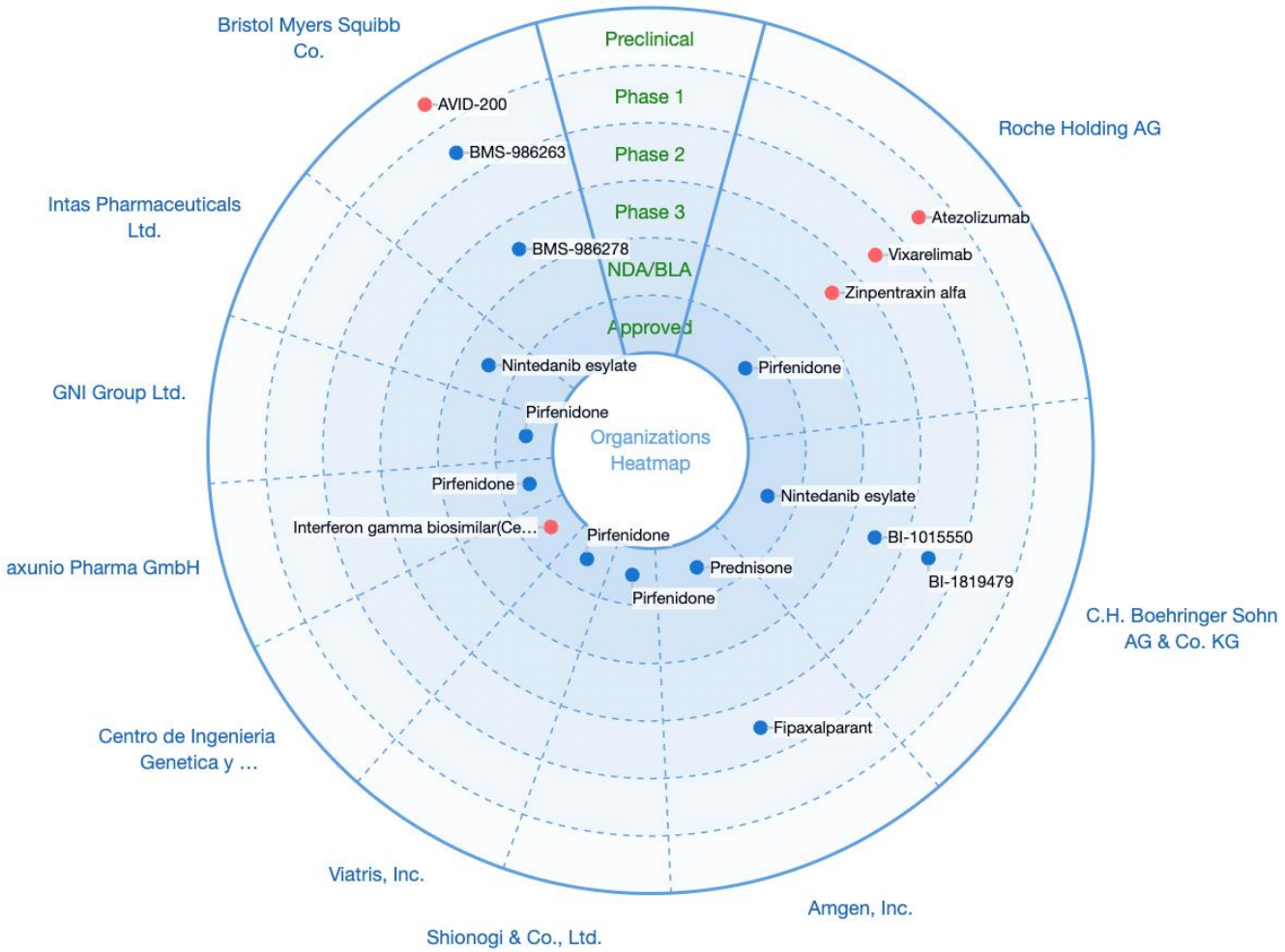
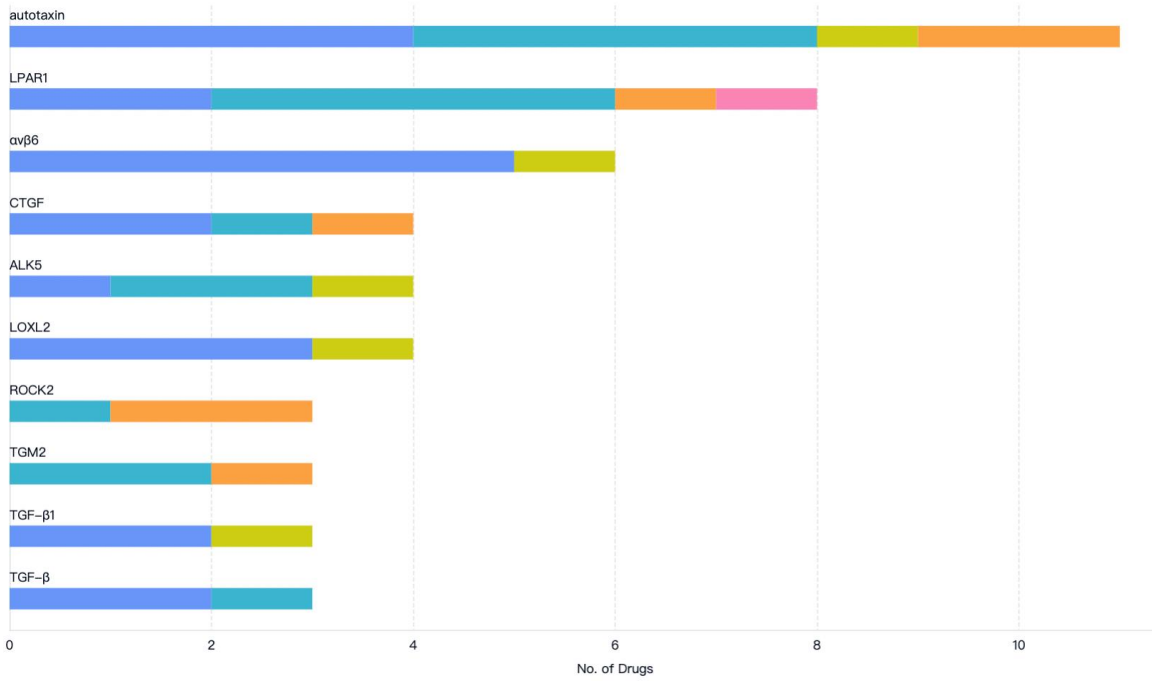


Figure 16. *Global statistics on drug research (chemicals and biologicals) in IPF.*

Caption:
Chemical drugs = blue circle
Biological products = red circle
Source: Synapse Database (2024)



Source: Synapse Database (2024)

Figure 17. *The ten most popular targets investigated for the treatment of IPF.*

Table 6. *Summary of potential treatments for IPF.*

TITLE	TARGET OR FACTOR ASSOCIATED WITH IPF IDENTIFIED	THERAPY OR MEDICATION
Lysophophatidic acid receptor 1 inhibition: a potential treatment target for pulmonary fibrosis	Lysophosphatidic acid (LPA)-mediated activation of LPA receptor 1 (LPAR1); and the LPA-producing enzyme autotaxin (ATX) and activation of LPAR1	Signaling in pulmonary fibrosis and to help differentiate new inhibitors in development
Targeting Alveolar Repair in Idiopathic Pulmonary Fibrosis	reparative epithelial progenitor cells in the alveolar region of the lung	Endogenous alveolar repair
The Bright side of fibroblastic: molecular signature and regenerative cues in major organs	The bright side of fibroblasts: molecular signature and regenerative signals in major organs: updated overview of fibroblast-derived regenerative signaling in different organs and discuss how this capacity may be compromised with aging	We also introduce a new paradigm for regenerative therapies based on the reversion of adult fibroblasts to a fetal/neonatal-like phenotype.
Target tumor suppressor p53 for organ fibrosis therapy	Tumor suppressor p53 (p53), known for its regulatory role in cell proliferation, apoptosis, aging and metabolism in various tissues	Development of strategies targeting p53 for the treatment of organ fibrosis
The Inflammasome NLR Family Pyrin Domain-Containing Protein 3 (NLRP3) as a Novel Therapeutic Target for Idiopathic Pulmonary Fibrosis	NLR family pyrin domain-containing protein 3 (NLRP3), once activated, promotes the production of IL-1β, IL-18, and innate immune responses.	Inhibition of NLRPP3 may offer a promising approach against the fibrotic process in the lungs
Pharmacological expansion of type 2 alveolar epithelial cells promotes regenerative lower air repair	Dipeptidyl peptidase 4 (DPP4) inhibitors selectively expand AEC2s (alveolar epithelial cells type 2 are stem cells in the adult lung that contribute to lower airway repair) and are broadly effective in several mouse models of lung injury.	Z-97, a persistent, locally administered pulmonary DPP4 inhibitor that broadly promotes efficacy in mouse lung injury models with minimal peripheral exposure and good tolerability.
US patent (US-12053477-B2) covers brilaroxazine in treating	Dopamine and serotonin play important roles in regulating processes such as fibrosis (scarring) and inflammation.	Brilaroxazine is a new chemical entity designed to modulate the activity of

TITLE	TARGET OR FACTOR ASSOCIATED WITH IPF IDENTIFIED	THERAPY OR MEDICATION
IPF, like diseases		dopamine and serotonin receptors, two key signaling molecules
Idiopathic Pulmonary Fibrosis: Addressing the current and future therapeutic advances along with the role of Sotatercept in the management of pulmonary hypertension	Inhibition of several tyrosine kinases decreases the proliferative activities that lead to fibrosis.	Saracatinib is a tyrosine kinase inhibitor that primarily targets the SRC protein, potentially used to treat diseases such as pulmonary fibrosis by inhibiting fibroblast activity and collagen deposition, while Sotatercept is a fusion protein used to treat pulmonary arterial hypertension (PAH) by targeting specific pathways that contribute to abnormal blood vessel growth in the lungs;
Promising advances in treatments for the management of idiopathic pulmonary fibrosis	Presents a collection of phase 3 tests: Targets: PDe4B; Fibroblast activities; CTGF; Innate immune response; Lung microbiome	"BI 1,015,550; Inhaled treprostinil; Pamrevlumab
Innovative Pre-Clinical Data Using Peptides to Intervene in the Evolution of Pulmonary Fibrosis	Immunomodulatory peptides ToAP3 and ToAP4	Immunomodulatory peptides ToAP3 and ToAP4: both peptides controlled experimental IPF, maintaining tissue characteristics and standard functional properties and regulating the production of cytokines associated with fibrosis. The data obtained in this work show that the regulation of the immune response by ToAP3 and ToAP4 can control the alterations that cause the fibrotic process, making both peptides potential therapeutic alternatives and/or adjuvants for IPF.
Administration of Collagen Peptide Prevents the Progression of Pulmonary Fibrosis in Bleomycin-Treated Mice	Peptide collagen	The present study showed that administration of peptide collagen derived from chicken feet suppressed the progression of Pulmonary Fibrosis in mice.
Exploring Therapeutic targets for molecular therapy of idiopathic pulmonary fibrosis	Transforming growth factor beta, vascular endothelial growth factor, platelet-derived growth factor, fibroblast growth factor, lysophosphatidic acid, interleukin-13, Rho-associated coiled-coil forming protein kinase family, and Janus kinases/signal transducers and activators of transcription pathway.	Transforming growth factor beta, vascular endothelial growth factor, platelet-derived growth factor, fibroblast growth factor, lysophosphatidic acid, interleukin-13, Rho-associated coiled-coil forming protein kinase family, and Janus kinases/signal transducers and activators of transcription pathway.
Turning the tide: From fibrosis to regeneration following anti-fibrogenic cell vaccination	ADAM12, a member of the A Disintegrin and Metalloprotease (ADAM) family of proteins that harbors extracellular metalloprotease and intracellular signaling properties. ADAM12 is an interesting target because tissue-resident ADAM12+ cells have been identified as the source of most a-SMA+ myofibroblasts generated after acute muscle and dermal injury, and its expression is largely limited to the embryonic period. GLI1 is expressed in mesenchymal cells after injury, giving rise to a-SMA+ myofibroblasts after tissue injury	Novel immunotherapeutic vaccine approach to target fibrotic lesions in models of liver and lung fibrosis: (This therapeutic strategy is similar to a cancer vaccine approach, but instead of targeting tumor-specific antigens, it targets fibrogenic cell-specific antigens.) Vaccination with a lentiviral vector encoding Gli1 abrogates bleomycin-induced lung fibrosis
A small-molecule TNIK inhibitor targets fibrosis in preclinical and clinical models	It was identified TRAF2- and NCK-interacting kinase (TNIK) as an antifibrotic target using a predictive artificial intelligence (AI) approach.	"INS018_055, a small molecule TNIK inhibitor, was generated, which exhibits desirable drug-like properties and antifibrotic activity in different organs in vivo via oral, inhaled or topical administration. INS018_055 possesses anti-inflammatory

TITLE	TARGET OR FACTOR ASSOCIATED WITH IPF IDENTIFIED	THERAPY OR MEDICATION
		effects in addition to its antifibrotic profile, validated in multiple in vivo studies.

Source: Authors

This period of articles studied includes a large number of potential treatments for IPF, in progress. From pharmacotherapy to regenerative therapies. Greater understanding of the significant involvement of lung epithelial cells in IPF leads to the investigation of novel approaches to target lung epithelial repair. The approaches are defined according to the targets identified and associated with the IPF. Figure 16 presents the global drug research statistics for IPF according to the Synapse database and figure 17 presents the ten most popular drug targets currently investigated for the treatment of IPF, extracted from the same database [39]. Table 6 presents a summary of potential treatments [7, 8, 12, 13, 33, 35, 36, 42, 45], containing the therapy or drug and the target or factor associated with IPF identified, including the innovative immunotherapeutic vaccine approach to target fibrotic lesions. Figure 18 shows the scheme of this immunotherapeutic vaccination against proteins restricted to fibrogenic cells, which results in fibrogenic cell death and regeneration of the parenchyma [27]. Among the articles studied, a testing methodology using a predictive artificial intelligence (AI) approach also stands out [30]. Figure 19 presents this methodology. The class of molecular medicines currently in clinical trials or that have been completed is presented in table 7 [20].

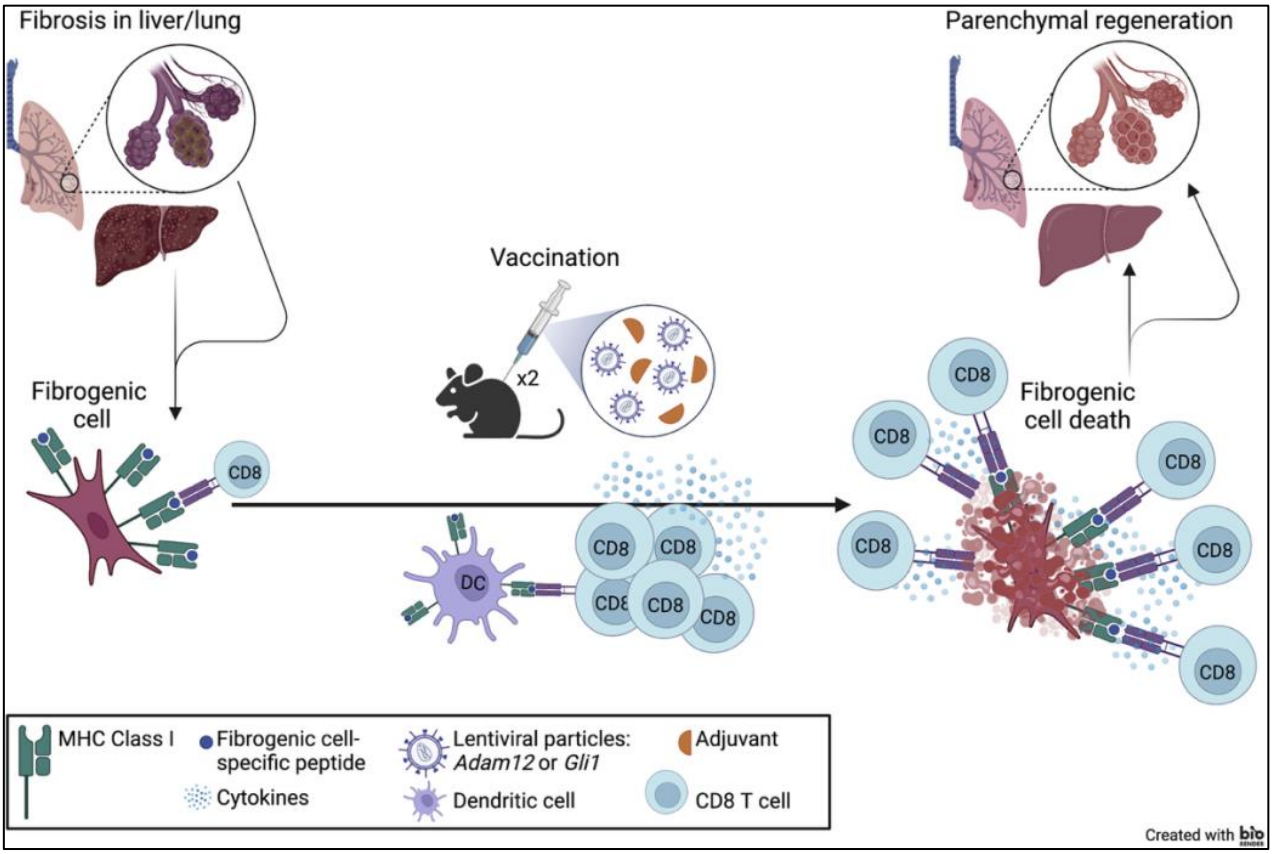


Figure 18. *Scheme of immunotherapeutic vaccination.*

Immunotherapeutic vaccination against fibrogenic cell-restricted proteins results in fibrogenic cell death and parenchymal regeneration Source: Phadke, Dwivedi, Taylor (2022).
Source: Phadke, Dwivedi, Taylor (2022)

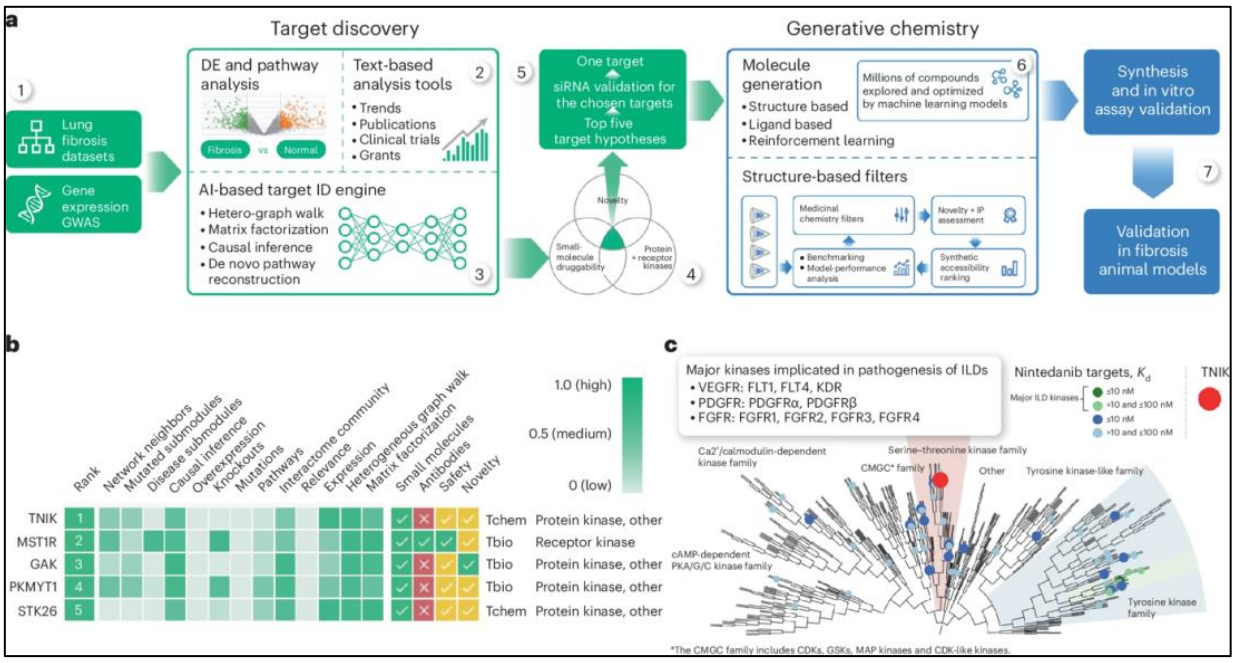


Figure 19. *Predictive Artificial Intelligence (AI) approach to identify antifibrotic target.*

a- The PandaOmics target discovery platform was applied to lung and kidney fibrosis datasets to generate target hypotheses, followed by application of the Chemistry42 platform to generate small molecule leads targeting TNIK. DE, differential gene; GWAS, genome-wide association study; hetero, heterogeneous; siRNA, small interfering RNA; IP, intellectual property. b- TNIK was ranked as the number 1 candidate using PandaOmics protein and receptor kinase settings based on relatively high values of network neighbors, mutated submodules, causal inference, pathways, interactome community, expression, heterogeneous graph walk, and matrix factorization scores. GAK, cyclin G-associated kinase; MST1R, macrophage-stimulating receptor 1; PKMYT1, protein kinase, membrane-associated tyrosine-threonine 1; STK26, serine-threonine kinase 26; Tchem, genes whose products can be targeted with small molecules better than the following bioactivity cutoffs: 30 nM for kinases, 100 nM for GPCRs and nuclear receptors, 10 μM for ion channels, and 1 μM for other target classes; Tbio, genes annotated with a Gene Ontology Molecular Function or Biological Process with an Experimental Evidence code, or targets with confirmed OMIM phenotype(s), or do not meet the Tdark criteria.

c- TNIK is a member of the STE20 serine-threonine kinase family. This family does not contain any important antifibrotic drug targets, including Nintedanib, the most prominent kinase inhibitor used in the treatment of IPF. This illustrates the relative novelty of the target. cAMP, cyclic AMP; FLT, FMS-related receptor tyrosine kinase 1; GSK, glycogen synthase kinase; KDR, kinase insert domain receptor; MAP, mitogen-activated protein; PKA, protein kinase A; ILD, interstitial lung disease; Kd, dissociation constant.

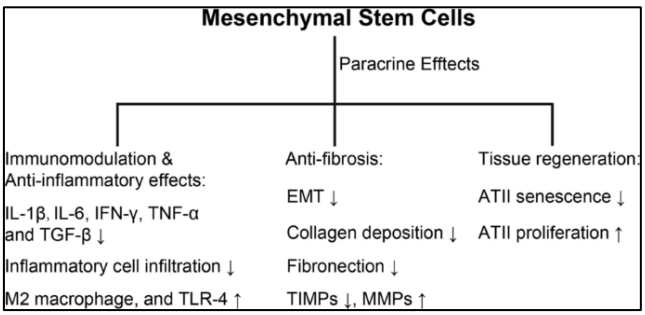
Source: Ren, et al. (2024)

Table 7. *Molecular medicines that are currently in clinical trials or that have been completed and their corresponding information.*

Target molecule	Drug or treatment	Administration route	Clinical trial stage	Research type	Patients number	Outcomes
galectin-3	TD139, a galectin-3 inhibitor	Inhalation, 0.3, 3, or 10 mg for 14 days	I/IIa	Double blinded, Randomized	24 patients. Each cohort: TD139 (n = 5) or placebo (n = 3)	Inhibition of Gal-3 expression in the lung was associated with reductions in plasma biomarkers (TD139 groups compared with placebo).
αvβ6 integrin	BG00011, a humanized monoclonal antibody against αvβ6 integrin	Subcutaneous, 56 mg once weekly	IIb	Double blinded, Randomized	106 patients. BG00011 (n = 54) or placebo (n = 52)	No significant difference in FVC change from baseline between patients who received BG00011 or placebo at week 26.
CTGF	Pamrevlumab, a recombinant human antibody that binds to	Intravenous, 30 mg/kg, every 3 weeks over 48	III	Double blinded,	356 patients.	Study did not meet its primary endpoint.

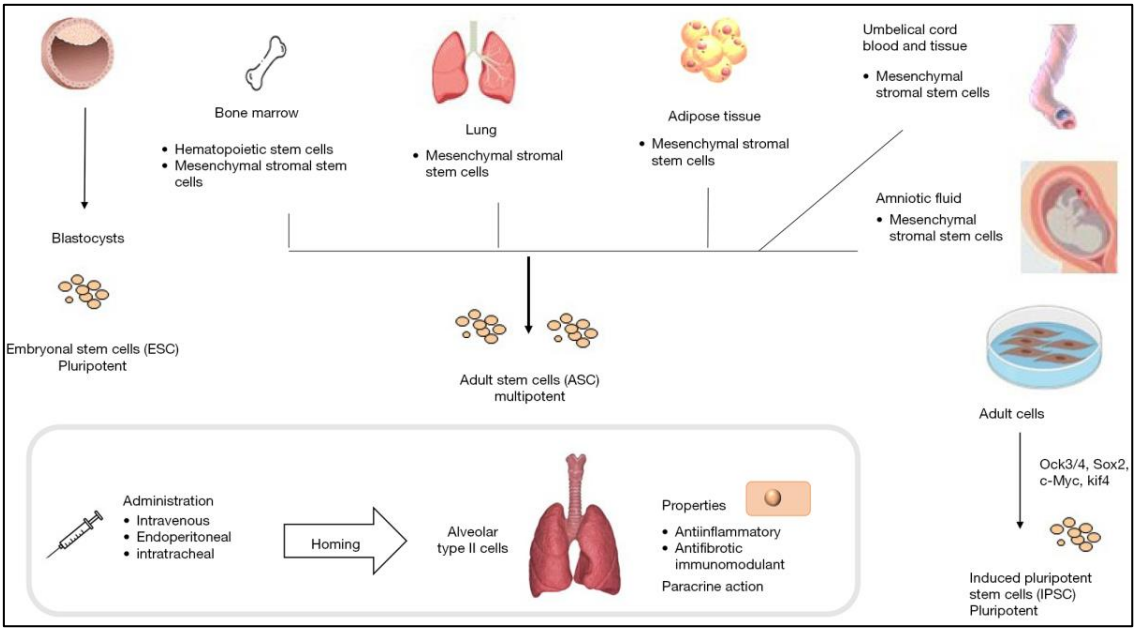
Target molecule	Drug or treatment	Administration route	Clinical trial stage	Research type	Patients number	Outcomes
	CTGF	weeks		Randomized		
LPA receptor	BMS-986020 (Bristol-Myers Squibb), an antagonist of the lysophosphatidic acid (LPA) receptor 1 (LPA1)	Oral, 600 mg, once/twice daily for 26 weeks	II	Double blinded, Randomized	143 patients. placebo (n = 47), 600 mg qd (n = 48), 600 mg bid (n = 48)	Patients treated with BMS-986020 experienced a significantly slower rate of decline vs placebo in FVC at week 26.
Autotaxin (the primary enzyme responsible for the production of LPA)	GLPG1690 (Galapagos, Mechelen, Belgium), a selective inhibitor of autotaxin	Oral, 600 mg/200 mg once daily for at least 52 weeks	III	Double blinded, Randomized	1306 patients.	GLPG1690 did not improve clinical outcomes compared with placebo.
IL-13	Lebrikizumab, a monoclonal antibody inhibits the secretion of IL-13	Subcutaneous, 250 mg, every 4 weeks	II	Double blinded, Randomized	505 patients. In cohort A, 154 patients, lebrikizumab (n = 78) or placebo (n = 76). In cohort B, 351 patients received pirfenidone, lebrikizumab (n = 174) or placebo (n = 177)	The predicted decline of the annualized rate of FVC% was not met.
IL-4 and IL-13	SAR156597, a monoclonal antibody targeting IL-4 and IL-13	Subcutaneous, 200 mg once a week or once every 2 weeks	IIb	Double blinded, Randomized	325 patients, placebo (n = 109), SAR156597 Q2W (n = 108), SAR156597 QW (n = 108)	SAR156597 failed to demonstrate benefit in treating IPF patients.
Rho-associated protein kinase 2 (ROCK2)	KD025 (or SLX-2119; Kadmon Corporation, Belumosudil), a selective ROCK2 inhibitor	Oral, 400 mg once a week	II	Open-label, Randomized	76 patients. KD025 (n = 52) or best supportive care (n = 24)	KD025 reduced the decline of FVC by 73% versus patients receiving supportive care at week 24.

FVC: forced vital capacity; TGF-β1: transforming growth factor-β1; CTGF: connective tissue growth factor; LPA: lysophosphatidic acid; IL: interleukin; ROCK2: Rho-associated protein kinase 2.
Source: Li, et al. (2024)



Source: Cheng, Zeng, Wang (2022)

Figure 20. *Mechanism of MSC-based therapy for IPF (MSC = mesenchymal stem cells).*



Source: Stella, et al. (2022)

Figure 21. *Different types of stem cells for the treatment of IPF.*

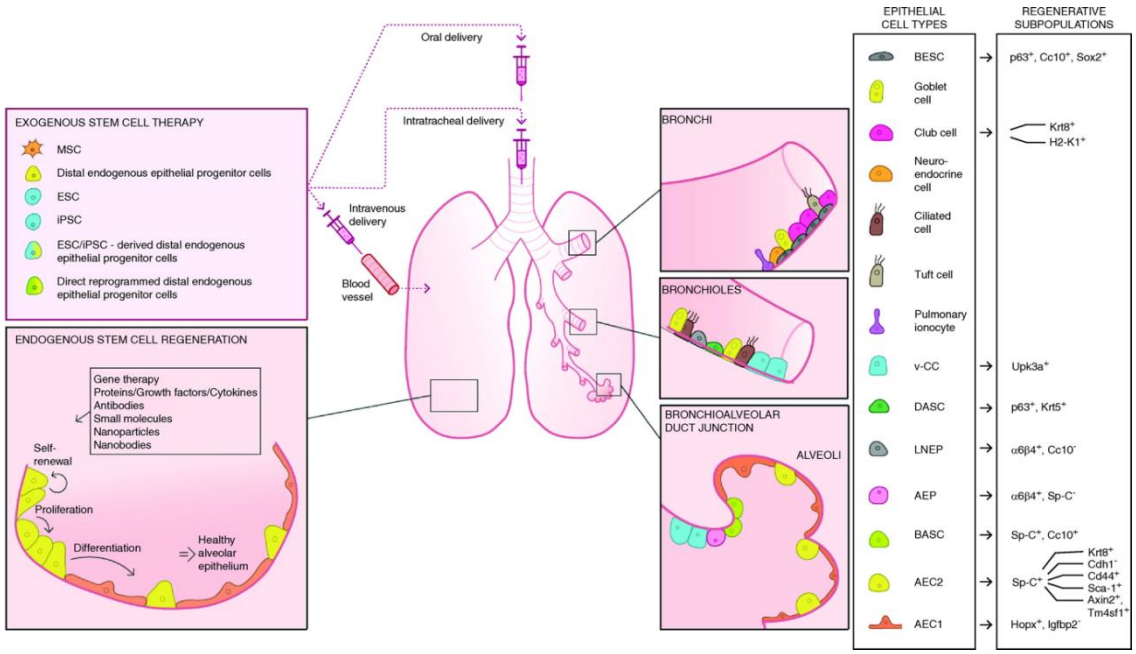


Figure 22. *Strategies to promote therapeutic lung regeneration in IPF.*

Strategies to promote therapeutic lung regeneration include exogenous administration of stem cells, including primary endogenous distal epithelial progenitor cells, multi- or pluripotent stem cells (MSCs, ESCs, iPSCs), stem cell-derived distal epithelial progenitor cells, and directly reprogrammed distal epithelial progenitor cells. Endogenous activation of distal epithelial progenitor cells to promote self-renewal, proliferation, and differentiation of the alveolar epithelium can be induced through modulation of the molecular environment (signaling pathways, extracellular matrix) or by directly targeting individual cell types.

Potential future therapies include gene therapy (oligonucleotide delivery and gene editing); administration of peptides such as growth factors, cytokines, and proteins; inhibition of receptors and targets with antibodies; and administration of small molecules, nanoparticles, and nanobodies designed for specific targets of interest. AEC1 = alveolar epithelial cell type 1; AEC2 = alveolar epithelial cell type 2; AEP = alveolar epithelial progenitor cell; BASC = bronchus alveolar stem cell; BESC = bronchial epithelial stem cell; DASC = distal airway stem cell Source: Ptasinski, et al (2021)

NO	Trail ID	Disease	Title	Inclusion criteria	No. Of patients	Cell type	Route	No of cells per infusion	No. of infusions	Safety outcome	Efficacy outcome	Phase	Locations
1	NCT02594839	IPF	First-in-human high-cumulative-dose stem cell therapy in idiopathic pulmonary fibrosis with rapid lung function decline (Averyanov et al., 2020)	Progressive IPF (FVC or DLco decline of≥10% dur- ing the last year, current FVC≥40%, current DLco≥20%)	20	Allogeneic BM-MSCs	IV	Group 1: 10 patients, 1.6×10^8 cells Group 2: 10 patients, placebo	Multiple infusions of 200×10^6 cells over 39 weeks	The main adverse reactions were mild fever and chills, and did not require study discontinuation.	FVC decline was significantly improved in the MSCs treatment group at 52 weeks (from −13.8% to +3.7%), as compared with the placebo group (from −11.7% to −9.5%). But, in the MSCs therapy group 4 patiengts had a continuing decline of FVC and DLco >10% over the observation period.	I/IIa	Russian Federation
2	NCT01919827	IPF	Endobronchial autologous bone marrow– mesenchymal stromal cells in idiopathic pulmonary fibrosis: a phase I trial (Campo et al., 2021)	mild-to-moderate IPF (FVC⩾50% predicted and DLco⩾35% pred)	13	Autologous BM-MSCs	Endobr- onchial infusion	(10–100)× 10^6 cells	Multiple infusions	No treatment-related severe adverse events were observed during follow-up.	Compared to baseline, the mean forced vital capacity showed an initial decline of 8.1% at 3 months. The number of patients without functional progression was six (46%) at 3 months and three (23%) at 12 months.	I	Spain
3	NCT01385644	IPF	A phase 1b study of placenta-derived mesenchymal stromal cells in patients with idiopathic pulmonary fibrosis (Chambers et al., 2014)	Moderate to severe disease (FVC≥50% DLco≥25% Honeycomb-ing>5% in≤3/6 lung zones	8	Allogene placenta-derived MSCs	IV	Group 1: 4 patients,1×10^6 cells Group 2: 4 patients,2×10^6 cells	Single-dose	Most adverse events were mild and self-limiting.	At 6 months FVC, DLco, 6 MWD and CT fibrosis score were unchanged compared with baseline.	Ib	Australia
4	NCT02013700	IPF	Allogeneic Human Mesenchymal Stem Cells in Patients With Idiopathic Pulmonary Fibrosis via Intravenous Delivery (AETHER): A Phase I Safety Clinical Trial (Glassberg et al., 2017)	Mild to moderate disease (FVC≥50% DLco≥30%)	9	Allogeneic BM-MSCs	IV	Group 1: 3 patients,2×10^7 cells Group 2:3 patients, 10^8cells Group 3: 3 patients,2×10^8 cells	Single-dose	There were no instances of treatment-emergent adverse events.	At 60 weeks after MSCs injection, there was a 3.0% mean decline in % predicted FVC and 5.4% mean decline in % predicted DLco.	I	United States
5	unknown	IPF	A prospective, non-randomized, non-placebo-controlled phase Ib clinical trial to study the safety of adipose derived stromal cells-stromal vascular fraction in idiopathic pulmonary fibrosis (Tzouvelekis et al., 2013)	Mild to moderate disease (FVC>50%,DLco>35%)	14	Autologous AD-MSCs	endobr- onchial infusions	5×10^5 cells/kg	3 infusions 1 month apart	Minor adverse events, mostly related to Bronchoscopy.	No fibrosis exacerbation	Ib	Greece
6	NCT05468502	IPF	Phase I/IIa Clinical Trial of Human Umbilical Cord Mesenchymal Stem Cell Injection in the Treatment of Idiopathic Pulmonary Fibrosis (IPF)	Mild to moderate disease ((FVC>50%,DLco>35%)	18	Allogeneic hUC-MSCs	endobr- onchial infusions	Group 1: 3 patients$6.0*10^6$ cells Group 2:3 patients, $3.0*10^7$ cells Group 3: 3 patients,6.0×10^7 cells Group 4: 3 patients$9.0*10^6$ cells	Single-dose	No results posted	No results posted	I/IIa	China
7	NCT05016817	IPF	Safety of Cultured Allogeneic Adult Umbilical Cord Derived Mesenchymal Stem Cell Intravenous Infusion for IPF	Diagnosis of Idiopathic Pulmonary Fibrosis	20	Allogeneic hUC-MSCs	IV	10^8 cells	Single-dose	No results posted	No results posted	I	Antigua and Barbuda Argentina Mexico
8	NCT03929120	ILD	Allogeneic Bone Marrow Mesenchymal Stem Cells for Patients With Interstitial Lung Disease (ILD) and Connective Tissue Disorders (CTD)	Patients with new diagnosis of ILD associated with CTD, ANCA associated vasculitis or IPAF or established diagnosis of ILD associated with CTD under conventional therapy for at least 6 months but less than 24 months, with no evidence of improvement.	10	Allogeneic BM-MSCs	IV	(0.5–1)$\times10^6$ cells/kg	Single-dose	No results posted	No results posted	I	United States

IPF, idiopathic pulmonary fibrosis; FVC, functional vital capacity; DLco, diffusing capacity of the lung for carbon monoxide; BM-MSCs, bone marrow-derived mesenchymal stem cells; IV, intravenous; AD-MSCs, adipose-derived mesenchymal stem cells; hUC-MSCs, human umbilical cord derived mesenchymal stem cells; CTD, connective tissue disorders; ILD, interstitial lung disease; ANCA, antineutrophil cytoplasmic antibodies; IPAF, idiopathic pneumonia with autoimmune features; 6MWT, 6-min walk test; CT, computed tomography.

Source: Yang, et al (2023)

Figure 23. *Summary of current clinical trials on MSCs and MSC-EVs (Extracellular Vesicles) for IPF.*

Given the references found, which are of high relevance within regenerative medicine, the mechanism of stem cell-based therapy is presented [44]. This group includes endogenous lung stem/progenitor cells, embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs) and mesenchymal stem cells (MSCs). MSCs harbor injured lungs, where they exert immunomodulatory and antifibrotic effects through paracrine actions and activate endogenous lung stem cells to promote regeneration of injured lungs. MSCs are currently the most commonly used stem cells in clinical trials due to their low immunogenicity and tumorigenicity and absence of potential ethical problems. Figure 20 illustrates the mechanism of MSC-based therapy for IPF [11], Figure 21 presents the classification of different stem cells and their application for the treatment of IPF [38], and finally Figure 22 presents strategies to promote therapeutic lung regeneration [28].

Also noteworthy is the presentation of randomized clinical studies that evaluate lung stem cell transplantation for IPF, namely the AETHER study and the HALT-IPF study. In the trial, allogeneic human mesenchymal stem cells (MSCs) were introduced into patients with idiopathic pulmonary fibrosis intravenously (AETHER), bone marrow-derived MSCs were administered intravenously to patients with rapidly progressive IPF who were not receiving antifibrotic medications. The study demonstrated promising results, safety and tolerability of this treatment. Another study, Autologous Human Lung Stem Cell Transplantation for IPF (HALT-IPF) (NCT04262167), is currently ongoing. A summary of preclinical and clinical studies exploring the application of MSCs from different sources in the treatment of IPF is shown in Figure 23 [44].

Other regenerative medicine approaches include tissue engineering. There is a need for improved three-dimensional (3D) lung models that recapitulate the architectural and cellular complexity of the native lung alveolus. These three-dimensional models provide a broad spectrum of applicability and mimicry of the lung microenvironment, assisting in research into the treatment of IPF, such as the search for new drugs, which can then be safely tested before evolving into the patient. Figure 24 shows a schematic of the preparation of engineered lung tissue [18].

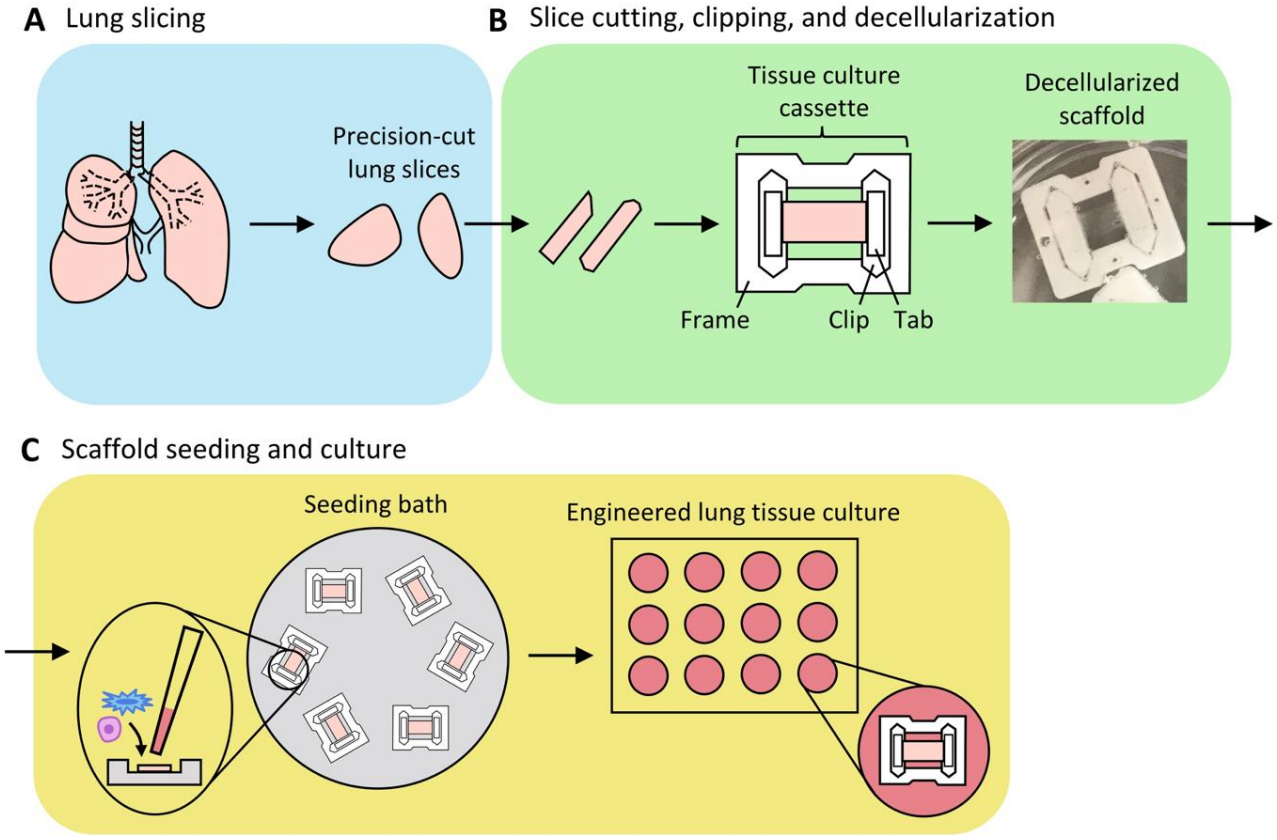


Figure 24. *Schematic of the preparation of engineered lung tissue.*

A) Native lung tissue is cut into slices using a vibratome. (B) Precision-cut lung slices are cut into standardized 3-mm-wide strips, cut into polytetrafluoroethylene (PTFE) tissue culture cassettes, and decellularized with detergent to produce acellular extracellular matrix scaffolds. (C) The scaffolds are reseeded in specialized seeding baths that confine the seeding area to the tissue area, and then cultured in a standard well plate Source: Leiby, et al. (2022)

Last but not least, this period of studied references details the use of the concept of Precision Medicine for the treatment of IPF. Within this concept are the following focuses: Personalized medicine approaches, such as the identification of qualified diagnostic, prognostic and predisposition biomarkers, as well as reliable indicators of pathogenic processes, the incorporation into clinical practice of new emerging genomic techniques and molecular tools. By incorporating these Precision Medicine approaches, therapeutic decision-making and treatment effectiveness will be improved, thus representing a crucial tool in the management of IPF.

Despite important recent advances in understanding the genetic risks underlying the diseases, current IPF guidelines have not yet included a recommendation for the use of genetic testing for diagnosis. This is still limited to the identification of a pattern of interstitial pneumonia based on radiological or histological criteria. It is worth noting that these criteria remain important, including in the field of radiology, with an article presenting a study on the assessment of the erector spinae muscle cross-sectional area (ESMCSA) by computed tomography. This study aims to confirm whether serial changes in ESMCSA are associated with survival in patients with IPF. Early decrease in ESMCSA may be a useful predictor of prognosis in patients with IPF. Figure 25 shows representative computed tomography images used to measure ESMCSA [25].

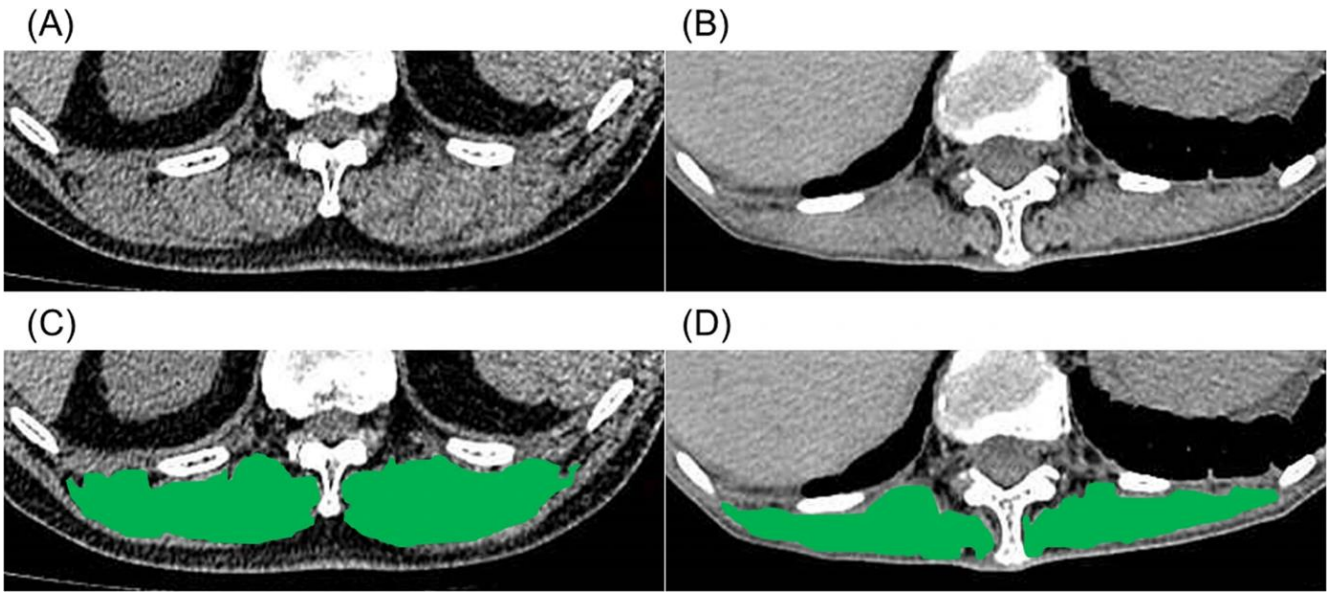


Figure 25. *Representative computed tomography images used to measure the cross-sectional area of the erector spinae muscles (A, B).*

The cross-sectional area of the erector spinae muscles. Representative computed tomography images used to measure the cross-sectional area of the erector spinae muscles (A, B). The cross-sectional areas of the erector spinae muscles are in green (C, D). The sum of the areas of the erector spinae muscles was 55.8 cm^2 (A, C) and 14.9 cm^2 (B, D).
Source: Nakano, et al (2020)

The American Thoracic Society (ATS), the European Respiratory Society (ERS), the Japanese Respiratory Society (JRS), and the Latin American Association of Thorax (ALAT) have recently updated clinical practice guidelines for IPF. However, they have not provided recommendations on when to perform genetic testing in patients or how to use these results in clinical practice.

Genetic sequencing of familial pulmonary fibrosis cases is already incorporated into routine clinical practice in several European countries, however, many centers have not yet incorporated genetic sequencing into interstitial lung disease (ILD) services, as an adequate international consensus has not yet been established. An international, multidisciplinary task force of experts (pulmonologists, geneticists, pediatricians, pathologists, genetic counselors, patient representatives and librarians) reviewed the literature between 1945 and 2022 and reached a consensus on all the following questions, as well as their answers, as shown in Figure 26 below: [9].

	Narrative questions addressed by the Task Force	Suggested Narrative
1	Which patients may benefit from genetic sequencing and clinical counselling?	Any patient with fibrotic ILD and one or more first- or second-degree family members with fibrotic ILD
		Any patient with a relative carrying a pathogenic/likely pathogenic variant known to cause ILD
		Any patient with suspected short telomere syndrome
		Any patient with an idiopathic fibrosing ILD before the age of 50 years
2	What is known on the natural history of FPF (with or without evidence of genetic mutation)?	Familial or monogenic fibrotic ILD in adults is usually progressive and frequently associated with a poor prognosis, independently of disease entity.
		In children, ILD is usually monogenic and disease course is dependent on the involved gene and mutations.
3	Which genes are usually tested?	Telomere- and surfactant-related genes are usually analysed.
		Targeted genetic sequencing of other genes can be discussed on a case-by-case basis, depending on the phenotype, and are beyond the scope of this paper.
4	What is the evidence for telomere length measurement?	Telomere length sometimes provides additional information to genetic sequencing and is sometimes performed when available in suspected telomere-related disease.
5	What is the role of common genetic variants (polymorphisms) in the diagnostic workup?	Pending new studies, the majority of Task Force members do not include the common genetic variants associated with IPF or FPF in the genetic diagnostic workup.
6	What are the optimal treatment options for FPF?	For patients with IPF or progressive pulmonary fibrosis (despite standard management), including those with FPF or a known monogenic disease, the Task Force agrees with current international guidelines recommending antifibrotic drugs.
		Treatment of childhood ILD is essentially based on expert opinion. Childhood ILD should be included in therapeutic trials when available.
		Task Force members would consider lung transplantation in patients with monogenic disease or FPF, when appropriate. In case of short telomere syndrome, the post-transplant immunosuppressive regimen should be carefully monitored and adjusted when indicated.
7	Which family members are eligible for genetic sequencing?	For families with proven monogenic disease, the Task Force supports offering genetic sequencing according to national directives or legislation.
8	Which clinical screening and follow-up parameters may be considered in family members?	The majority of Task Force members offer to all asymptomatic first-degree relatives of patients with FPF a periodic clinical evaluation for (early) ILD identification. Frequency is unknown at present.
		In their clinical practice, the majority of Task Force members advise all first-degree relatives of patients with FPF to have a chest CT scan and lung function tests at least when experiencing persistent respiratory symptoms, such as dyspnoea or cough.
		The majority of Task Force members include a complete blood count and hepatic enzyme evaluation in first-degree relatives of patients with short telomere syndrome.
		All known risk factors of pulmonary fibrosis such as smoking or other inhalational exposures should be avoided in first-degree relatives of patients with FPF.

Source: Borie, et al. (2023)

Figure 26. *Issues, by consensus, addressed by the task force and their respective suggestive narrative.*

The development and validation of evidence-based guidelines for genetic screening for IPF will allow us to redefine and classify this disease based on molecular characteristics and contribute to the implementation of precision medicine approaches. Figure 27 presents a schematic representation of personalized medicine approaches for patients with IPF [15]. Figure 28 presents current recommendations for genetic testing in IPF. Table 8 presents the markers for identifying pre-clinical disease in asymptomatic family members at risk [2].

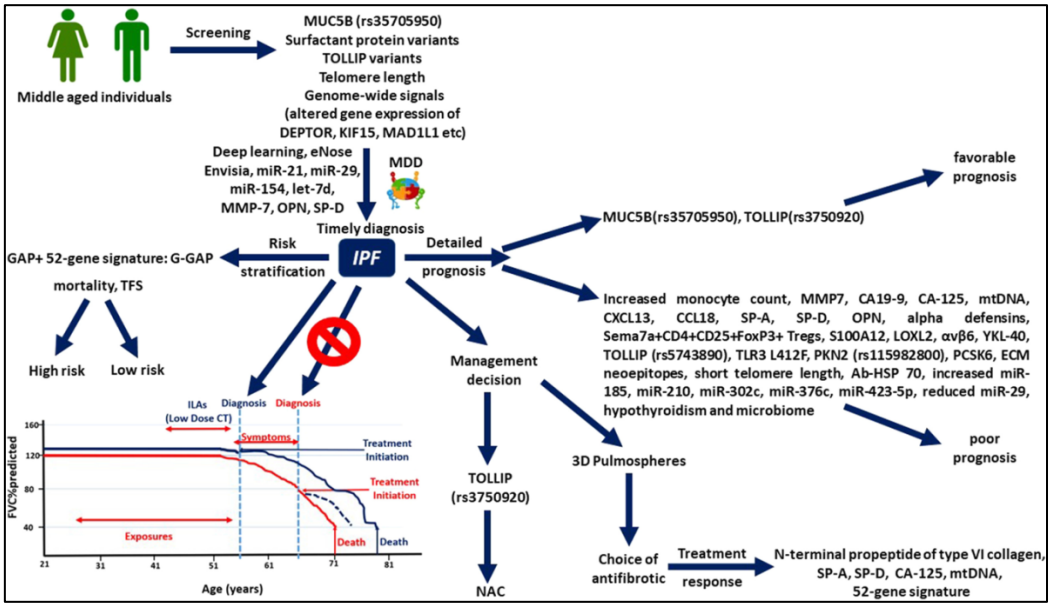


Figure 27. *Schematic representation of personalized medicine approaches for patients with IPF.*

Schematic representation of personalized medicine approaches that could be implemented in future clinical practice for patients with IPF. Early screening could lead to timely diagnosis, alter the natural course of the disease (red demarcation), and improve outcomes (blue demarcation). Implementation of the 52-gene signature could considerably improve the prognostic performance of the GAP index. A multitude of other biomarkers could have prognostic and/or theragnostic roles.
Source: Karampitsakos, et al. (2023)

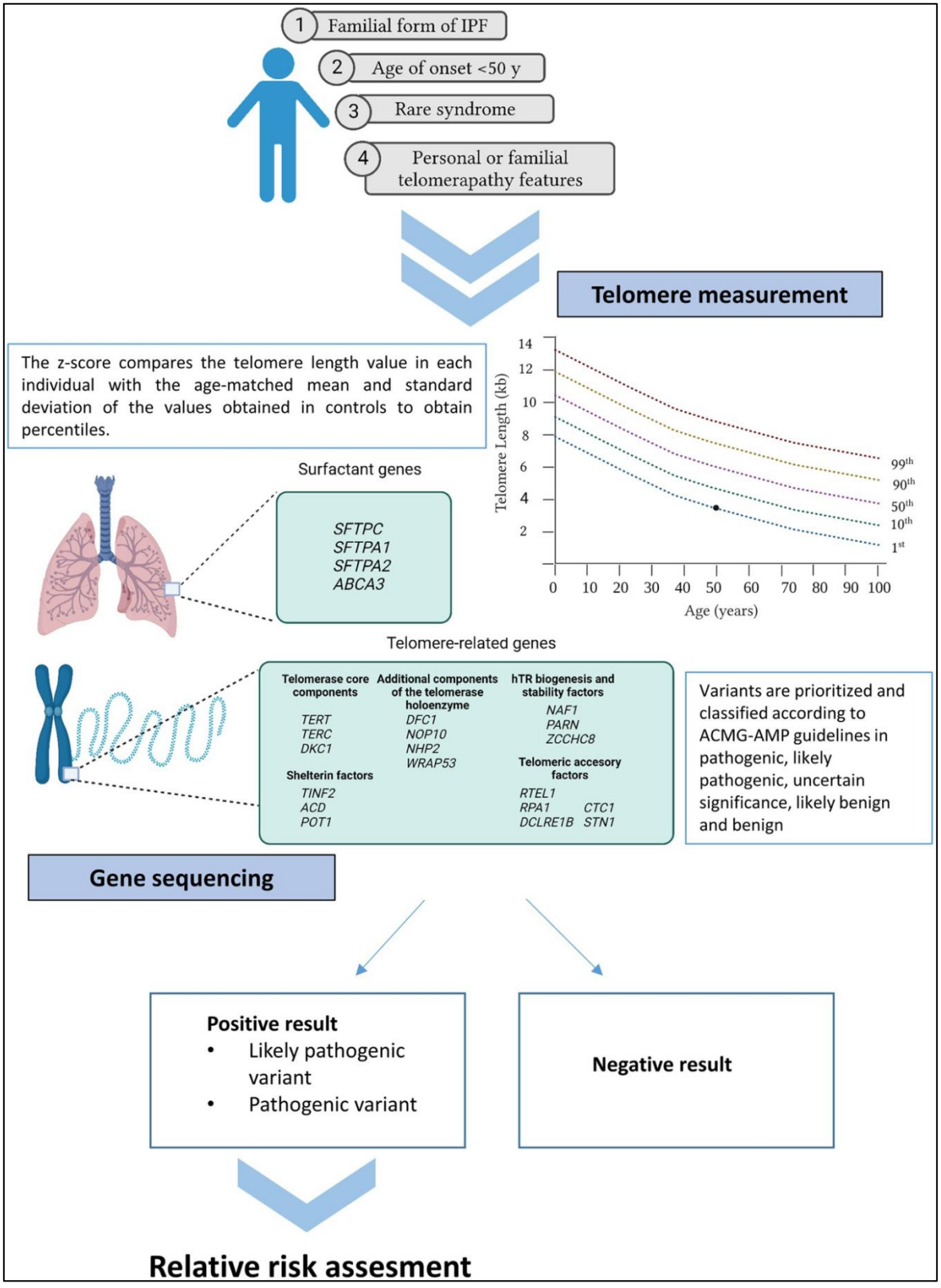


Figure 28. *Current recommendations for genetic testing in IPF.*

Current recommendations for genetic testing in IPF. Patients who meet at least one of the above criteria may benefit from genetic testing (telomere length measurement and gene sequencing). If a positive result is obtained, early family members may benefit from genetic analysis upon request.

Source: Gonzalez, et al (2023)

Table 8. *Markers for identifying preclinical disease in asymptomatic family members at risk.*

Pulmonary disease marker	Findings in screening asymptomatic relatives	Remarks from Task Force
Physical examination, symptoms		
Dyspnea/MRC-5	May be present; not predictive for pre-clinical pulmonary fibrosis	
Frequent cough	May be present; not predictive for pre-clinical pulmonary fibrosis	
Clubbing	May be present	
Inspiratory crackles	May be present	
Pulmonary function		Can be performed in subjects from age 6 years onward
FVC	Below normal values rare	
D_{LCO}	Below normal values may be present; lower in subjects with ILD changes than without ILD changes on HRCT	
TLC	Below normal values rare; lower in subjects with ILD changes than without ILD changes on HRCT	
Radiology HRCT	14–25% have ILD changes on HRCT or a diagnosis of ILD on first screening visit	One-third of *SFTPA1*/*SFTPA*2 mutation carriers may develop lung cancer
Genetic sequencing	Disease-causing variants in TRGs and SRGs	In families with a (likely) pathogenic SRG mutation: family members without the mutation are not at increased risk for FPF; in families with a (likely) pathogenic TRG mutation: family members without the mutation may have inherited short telomeres and may be at risk of development of STS
Extrapulmonary signs and symptoms of STS		In all families with unknown cause or TRG mutation
Hematological markers	Mean corpuscular volume above normal; red blood cells or platelets below normal	Abnormalities in one or several hematological cell lines are a sign of marrow dysfunction in asymptomatic carriers of TRG mutations
Liver enzymes	Elevated liver enzymes	Abnormalities in liver enzymes are a sign of hepatic disease in asymptomatic carriers of TRG mutations
Hair greying	Before 30 years of age	No consensual definition
Telomere length	<10th percentile	Low values for age associate with marrow dysfunction in asymptomatic carriers of TRG mutations

MRC: Medical Research Council; FVC: forced vital capacity; DLCO: diffusing capacity of the lung for carbon monoxide; TLC: total lung capacity; HRCT: high-resolution computed tomography; STS: short telomere syndrome; ILD: interstitial lung disease; TRG: telomere-related gene; SRG: surfactant-related gene; FPF: familial pulmonary fibrosis.
Source: Gonzalez, et al (2023)

Table 9. *Diagnostic and prognostic molecular biomarkers in IPF.*

Biomarker	Pathogenetic Process	Diagnostic	Prognostic	Specimen-
S100A4	Fibrogenesis	++	++	Serum

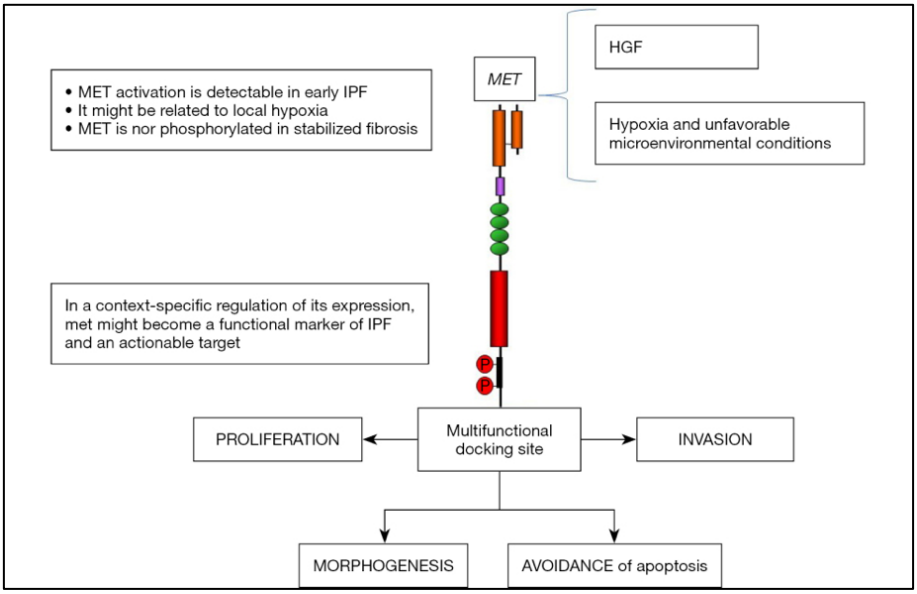
Biomarker	Pathogenetic Process	Diagnostic	Prognostic	Specimen-
				BALF Lung tissue
cCK-18	AECs apoptosis	+	-	Serum
KL-6	Alveolar epithelial marker	+	+++	Blood BALF
YKL-40	Adhesion molecule	-	++	Blood BALF Lung tissue
MMP-7	Extracellular remodelling	++	+++	Blood BALF Lung tissue
ICAM1	Adhesion molecule	-	++	Serum Blood
SPA & SPD	Alveolar epithelial markers	-	++	Serum
LOXL2	Extracellular matrix remodelling Fibrogenesis	-	+	Serum Lung tissue
Periostin	Extracellular matrix remodelling Fibrogenesis	-	+	Serum Lung tissue
CCL-18	Alternative alveolar macrophage activation	-	+	Serum BALF
IL-8	Potent chemotactic activity for polymorphonuclear leukocytes	-	+	Blood BALF
OPN	Inflammation Fibroblast migration and proliferation	-	+	Serum BALF Lung tissue
LC3β	Autophagy	-	+	Lung Tissue
BiP, XBP1	Unfolded protein response	-	+	Lung Tissue

Diagnostic and prognostic molecular biomarkers in IPF. The symbol '+++' is used when there is strong evidence and promising data supporting the potential role of the biomarker in the literature, whereas '++' is used when there are less promising data and '+' when there are contradictory data. The symbol '-' is used when there is no supporting evidence for such a potential role to date. Abbreviations: S100A4: S100 calcium-binding protein A4; cCK-18: caspase-cleaved cytokeratin-18; KL-6: Krebs von den Lungen-6; YKL-40: chitinase 3-like protein 1; MMP-7: matrix metalloproteinase-7; ICAM1: intercellular adhesion molecule 1; SP-A: surfactant protein A; SP-D: surfactant protein D; LOXL2: lysyl oxidase-like 2; CCL18: CC chemokine ligand 18; IL-8: interleukin 8; OPN: osteopontin; AECs: alveolar epithelial cells.
Source: Tomos, et al (2023)

Table 9 presents prognostic and diagnostic molecular biomarkers for IPF [41]. In figure 29 the oncogene factor MET is presented, as an actionable target for IPF. This factor, which is a gene that controls cell growth, division, and movement, is involved in many types of cancer. MET-mediated events in IPF depend on differences between physiological signals. MET blockade is one of the therapeutic strategies that aim to impair the "aberrant recapitulation of programmed development." The upregulation of MET induced by hypoxia may cooperate in triggering regenerative/reparative processes in IPF [38].

In such a challenging disease, the recognition of easy-to-measure peripheral blood biomarkers would facilitate immediate diagnoses, better prognoses and therapies that would promote the revival of the natural history of IPF, on the path to a cure.

The modulation of the pro-fibrotic environment in combination with the stimulation of endogenous reparative progenitor cells points to a possible treatment to promote lung regeneration, as well as the combination of stem cell therapy and gene therapy, which may offer new hope for the treatment of IPF, where, in figure 30, an example is illustrated [43].



Source: Stella, et al. (2022)

Figure 29. *MET oncogene factor as an actionable target for IPF.*

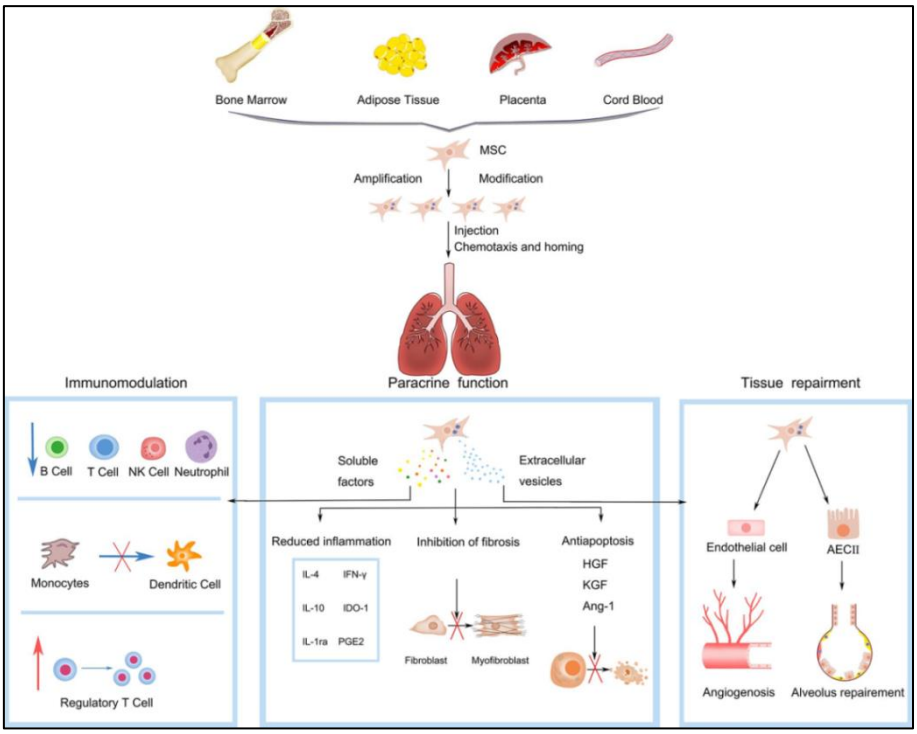


Figure 30. *Summary of therapeutic properties and mechanisms of mesenchymal stem cells in IPF.*

Mesenchymal stem cells (MSCs) gain chemotaxis and homing capabilities to the damaged lung by in vitro amplification and genetic engineering modification. The functions of MSCs in pulmonary fibrosis include: (1) Immunoregulation, interacting with multiple immune cells, such as T lymphocyte cells (T cells), natural killer (NK) cells, dendritic cells (DC), and B lymphocyte cells (B cells); blue arrows refer to inhibition, red arrows refer to promotion. (2) Paracrine function, secreting soluble factors and extracellular vesicles with inflammation-reducing (IL-10, IL-4, IL-1ra, IFN-γ, PGE2, IDO-1), anti-apoptotic (Ang-1, HGF, KGF), and anti-fibrosis functions. (3) Tissue repair, interacting with endothelial and epithelial cells to promote angiogenesis and alveolar repair. IL-10, interleukin-10; IL-4, interleukin-4; IL-1ra, IL-1 receptor antagonist; IFN-γ, interferon-γ; PGE2, prostaglandin E2; IDO-1, indoleamine 2,3-dioxygenase-1; Ang-1, angiogenin-1; HGF, hepatocyte growth factor; KGF, keratinocyte growth factor.

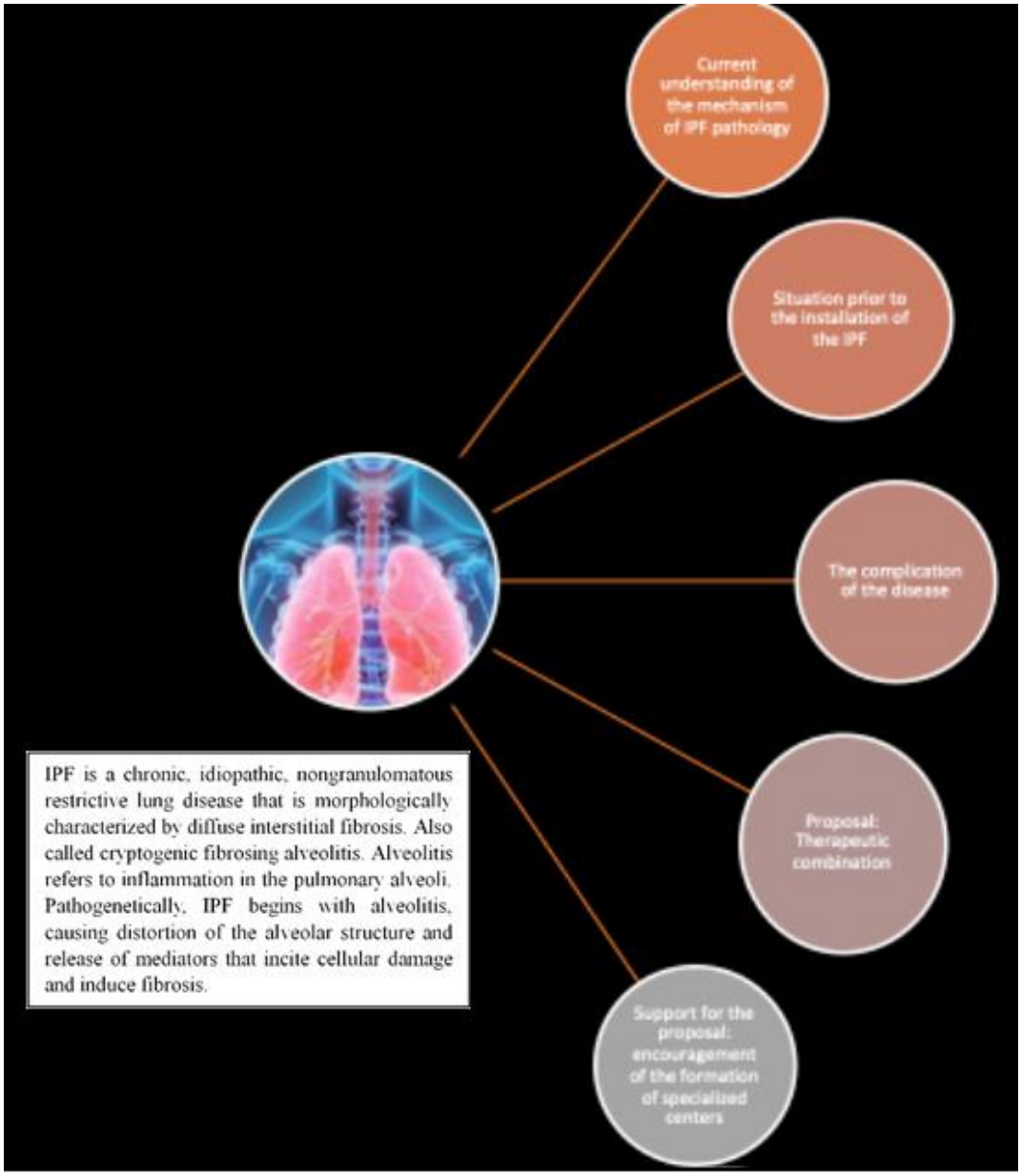
Source: Yang, et al. (2021)

Given the heterogeneity of IPF pathology, exhaustively exemplified in the literature analyzed, the updated

organization of a general treatment protocol is essential.

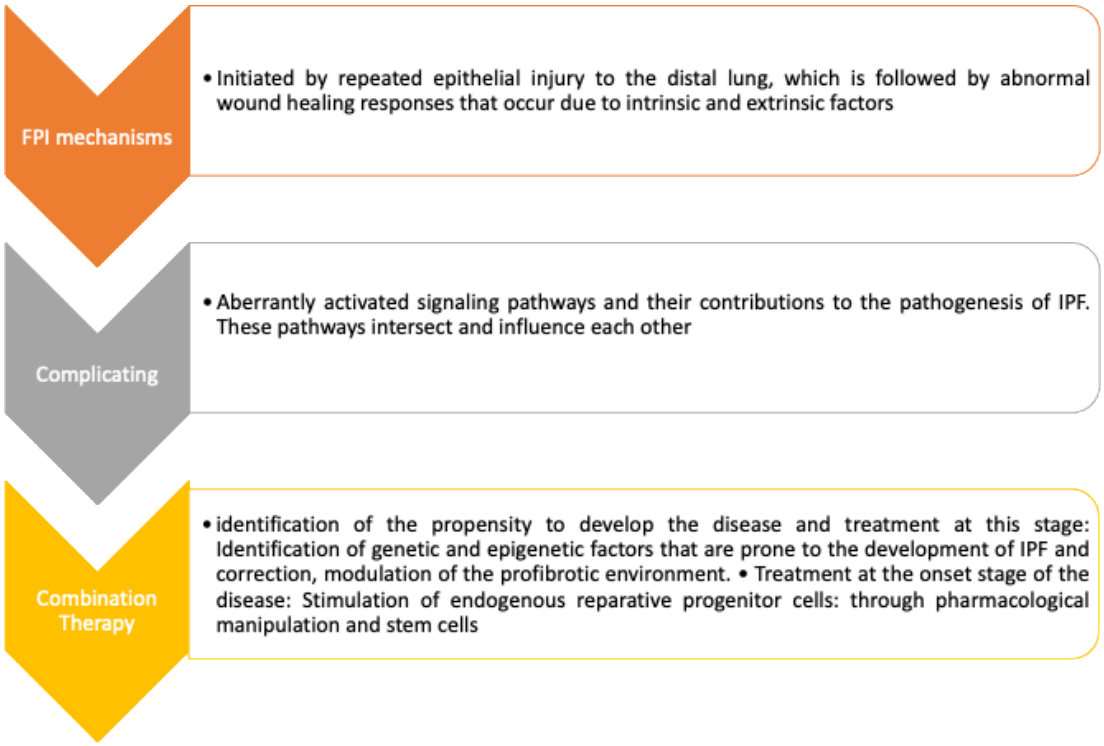
The diagnosis and treatment of patients with IPF require focused attention in specialized health centers (EHC), promoting close and flexible cooperation between pulmonologists, radiologists, biomedical geneticists, and pathologists, among others.

The authors of this work propose that the next general treatment protocol for IPF should include the two related perspectives of this pathology, namely: identification of the propensity for the development of the disease and treatment in this phase of assimilation and the second, which deals with the onset of the disease itself and, thus, clinical treatment in this stage. These two large groups are subdivided through the precision medical approach that adapts treatments to the characteristics of each patient, thus using the different treatment potentials presented in this literature review. Figure 31 has the ambitious intention of presenting a visual summary of this research on IPF, highlighting the definition, the current understanding of the scientific community, the aspect prior to the onset of the disease, which are the impactful genetic and epigenetic factors, the complicating factor that justifies the great difficulty of therapeutic cure, and culminates in the therapeutic proposition and its reinforcement, which are specialized and integrated health centers. Figure 32 presents the specific visual representation of the therapeutic proposal.



Source: Authors

Figure 31. *Visual representation of a summary of this research.*



Source: Authors

Figure 32. *Visual representation of a summary of mechanisms, complicating factors, and therapeutic combinations for IPF.*

4. Final Considerations

IPF is a disease that leads to fatal respiratory failure with progressive deterioration of gas exchange. Immunosuppressants have not demonstrated benefit in clinical trials and are currently considered inappropriate, while steroids are still used in the acute exacerbation phase.

The origins of this pathology remain undefined in some cases. Several factors contribute to its appearance, as presented in this review.

Extensive research into new ways to diagnose, treat and prevent IPF is ongoing and has been presented in this literature investigation.

Genetic and epigenetic factors were constantly highlighted as extremely necessary for the diagnosis.

Patients with IPF require focused attention in specialized health centers, promoting close and flexible cooperation of professionals.

The authors of this work propose that the next general therapeutic protocol for IPF should include, in the treatment guidelines, the two related perspectives of this pathology: identification of the propensity to develop the disease, through genetic tests and treatment of the patient, when the disease develops. By employing a precision medicine strategy, where treatments are tailored to individual patient characteristics, these two large groups are further divided, allowing for the utilization of the diverse treatment options highlighted in this literature review.

Abbreviations

IPF	Idiopathic Pulmonary Fibrosis
REC	Research Ethics Committee
FPF	Familial Pulmonary Fibrosis
ESCs	Embryonic Stem Cells
iPSCs	Induced Pluripotent Stem Cells
MSCs	Mesenchymal Stem Cells
EHC	Specialized Health Centers
ILD	Interstitial Lung Disease

Acknowledgments

The authors express their sincere appreciation to the institution Estacio de Sa University for support and greatly enhanced the quality and rigor of this research.

Funding

This work is not supported by any external funding.

Conflicts of Interest

The authors declare no conflicts of interest.

References

[1] AFYA BLOG GRADUATION. Regenerative Medicine: what it is and how it works? Brazil, Available at: https://graduacao.afya.com.br/medicina/medicina-regenerativa-o-que-e Accessed on: 11 June. 2024.

[2] ALONSO-GONZALEZ, A. *et al*. Idiopathic pulmonary fibrosis and the role of genetics in the era of precision medicine. Front Med (Lausanne), Spain, v. 27, n. 10, p. 1152211, abr./2023. Available at: https://doi.org/10.3389/fmed.2023.1152211

[3] AMARAL, Alexandre Franco; COLARES, P. D. F. B; KAIRALLA, Ronaldo Adib. Idiopathic Pulmonary Fibrosis: Current Diagnosis and Treatment. Brazilian Pneumological Journal, Brazil, v. 49, n. 4, p. 20230085, Aug./2023. Available at: https://jornaldepneumologia.com.br/details/3847/en-US/idiopathic-pulmonary-fibrosis--current-diagnosis-and-treatment (Accessed on: 8 July 2024).

[4] ARSHAD, Mahnoor; ATHAR, Zoraize Moeez; HIBA, Tasneem. Current and Novel Treatment Modalities of Idiopathic Pulmonary Fibrosis. Cureus, USA, v. 16, n. 3, p. 56140, March. /2024. Available at: https://doi.org/10.7759/cureus.56140

[5] BADDINI-MARTINEZ, J. et al. Update on the Diagnosis and Treatment of Idiopathic Pulmonary Fibrosis. Brazilian Pneumological Journal, Brazil, v. 41, n. 5, p. 454-466, Aug. 2015.

[6] BAO, Y. et al. Targeting tumor suppressor p53 for organ fibrosis therapy. Cell Death Dis, China, v. 15, n. 5, p. 336, May/2024. Available at: https://doi.org/10.1038/s41419-024-06702-w

[7] BHAT, Laxminarayan. Methods for treating pulmonary fibrosis.: Revive Pharmaceuticals, Inc. (Cupertino, CA). n. USA 20230061592 A1. Deposit 28 March. 2022. Concession: 02 March. 2023) Evaluation of Brilaroxazine (RP5063) in a Bleomycin-Induced Rodent Model of Idiopathic Pulmonary Fibrosis. https://doi.org/10.18103/mra.v11i4.3837

[8] BIANCATELL, R. M. L. C; SOLOPOV, Pavel A; CATRAVAS, John D. The Inflammasome NLR Family Pyrin Domain-Containing Protein 3 (NLRP3) as a Novel Therapeutic Target for Idiopathic Pulmonary Fibrosis. Am J Patho, USA, v. 192, n. 6, p. 837-846, jun./2022. Available at: https://doi.org/10.1016/J.AJPATH.2022.03.003

[9] BORIE, R. *et al*. European Respiratory Society statement on familial pulmonary fibrosis. European Respir J, France, v. 61, n. 3, p. 2201383, March /2023. Available at: 2025) https://doi.org/10.1183/13993003.01383-2022

[10] BUENO, M. et al. Mitochondria Dysfunction and Metabolic Reprogramming as Drivers of Idiopathic Pulmonary Fibrosis. Elsevier-Redox Biology, USA, v. 33, n. 101509, p. 32234292, March /2020. Available at: https://doi.org/doi.org/10.1016/j.rinp.2018.10.029

[11] CHENG, Wenzhao; ZENG, Yiming; WANG, Dachun. Stem cell-based therapy for pulmonary fibrosis. Stem Cell Therapy, China, v. 13, n. 1, p. 492, Oct./2022. Available at: https://doi.org/10.1186/s13287-022-03181-8

[12] GOMES, Rita N; MANUEL, Filipa; NASCIMENTO, Diana S. The bright side of fibroblasts: molecular signature and regenerative cues in major organs. NPJ Regen Med, Portugal, v. 6, n. 1, p. 43, Aug./2021. Available at: https://doi.org/10.1038/s41536-021-00153-z

[13] HADI, D. D. *et al*. Idiopathic pulmonary fibrosis: Addressing the current and future therapeutic advances along with the role of Sotatercept in the management of pulmonary hypertension. Immun Inflamm Dis, India, v. 11, n. 11, p. 1079, Nov./2023. Available at: https://doi.org/10.1002/iid3.1079

[14] IKRAMA, M. et al. Pulmonary fibrosis: Is stem cell therapy the way forward? J Taibah Univ Med Sci, Pakistan, v. 19, n. 1, p. 82-89, Oct./2023. Available at: https://doi.org/10.1016/j.jtumed.2023.09.009

[15] KARAMPITSAKOS, T. *et al*. Precision medicine advances in idiopathic pulmonary fibrosis. Ebio Medicine, USA, v. 95, n. 1, p. 104766, Sept./2023. Available at: https://doi.org/10.1016/j.ebiom.2023.104766

[16] KINOSHITA, Tomonari; GOTO, Taichiro. Molecular Mechanisms of Pulmonary Fibrogenesis and Its Progression to Lung Cancer: A Review. Int J Mol Sci., Japan, v. 20, n. 6, p. 1461, May/2019. Available at: https://doi.org/10.3390/ijms20061461 (Accessed on: 18 June. 2024).

[17] LECHNER, A. J.; MATUSCHAK, G. M.; BRINK, D. S. Lungs: An Integrated Approach to Disease. 1. ed. Brazil, Lange, 2013. p. 1-452.

[18] LEIBY, K. L. *et al*. Engineered Lung Tissues Prepared from Decellularized Lung Slices. J Vis Exp, USA, v. 21, n. 179, p. 179, Jan./2022. Available at: https://doi.org/10.3791/63151

[19] LEMOS, Carolina; RAOTA, T. M.; V. New Pharmacological Perspectives for the Treatment of Idiopathic Pulmonary Fibrosis: An Integrative Literature Review. Brazilian Medical Students Journal, Brazil, v. 8, n. 11, p. 352, Aug. 2023.

[20] LI, Y. et al. Exploring therapeutic targets for molecular therapy of idiopathic pulmonary fibrosis. Sci Prog, China, v. 107, n. 2, p. 368504241247402, April/2024. Available at: https://doi.org/10.1177/00368504241247402

[21] MA, H. *et al*. Research Progress in the Molecular Mechanisms, Therapeutic Targets, and Drug Development of Idiopathic Pulmonary Fibrosis. Front Pharmocol, China, v. 21, n. 13, p. 963054, July/2022. Available at: https://doi.org/10.3389/fphar.2022.963054

[22] MEI, Q. et al. Idiopathic Pulmonary Fibrosis: An Update on Pathogenesis. Frontiers in Pharmacology, China, v. 19, n. 12, p. 797292, Jan./2022. Available at: https://doi.org/10.3389/fphar.2021.797292

[23] MICHALSKI, Jacob E; SCHWARTZ, David A. Genetic Risk Factors for Idiopathic Pulmonary Fibrosis: Insights into Immunopathogenesis. J Inflammatory Res, USA, v. 5, n. 13, p. 1305, Jan./2021. Available at: https://doi.org/10.2147/JIR.S280958

[24] MURI, J. et al. Idiopathic Pulmonary Fibrosis: Review of Current Knowledge. Physiological Research, Slovakia, v. 73, n. 4, p. 487-497, March/2024. Available at: https://doi.org/10.33549/physiolres.935322

[25] NAKANO, A. *et al*. Early decrease in erector spinae muscle area and future risk of mortality in idiopathic pulmonary fibrosis. Sci Rep, Japan, v. 10, n. 1, p. 2312, Feb./2020. Available at: https://doi.org/10.1038/s41598-020-59100-5

[26] OLDHAM, Justin M; VANCHERI, Carlo. Rethinking Idiopathic Pulmonary Fibrosis. Clinics in Chest Medicine, USA, v. 42, n. 2, p. 263-273, June/2021. Available at: https://doi.org/10.1016/j.ccm.2021.03.005

[27] PHADKE, Ira; DWIVEDI, Alka; TAYLOR, Naomi. Turning the tide: From fibrosis to regeneration following anti-fibrogenic cell vaccination. Cell Stem Cell, USA, v. 29, n. 10, p. 1421-1423, Oct. 2022. https://doi.org/10.1016/j.stem.2022.09.007

[28] PTASINSKI, V. A. *et al*. Targeting Alveolar Repair in Idiopathic Pulmonary Fibrosis. Am J Respir Cell Mol Biol, England, v. 65, n. 4, p. 347-365, Oct./2021. Available at: https://doi.org/10.1165/rcmb.2020-0476TR

[29] REDDY, M. *et al*. Human Adipose-derived Mesenchymal Stem Cells Attenuate Early Stage of Bleomycin Induced Pulmonary Fibrosis: Comparison with Pirfenidone. International Journal of Stem Cells, India, v. 9, n. 2, p. 192-206, Nov./2016. Available at: https://doi.org/10.15283/ijsc16041

[30] REN, F. et al. A small-molecule TNIK inhibitor targets fibrosis in preclinical and clinical models. Nat Biotechnology, China, v. 43, n. 1, p. 63-75, March/2024. Available at: https://doi.org/10.1038/s41587-024-02143-0

[31] SELMAN, Moisés; PARDO, Annie. Revealing the pathogenic and aging-related mechanisms of the enigmatic idiopathic pulmonary fibrosis. an integral model. Am J Respir Crit Care Med., Mexico, v. 189, n. 10, p. 1161-1172, May/2014. Available at: https://doi.org/10.1164/rccm.201312-2221PP

[32] SGALLA, G. et al. Idiopathic Pulmonary Fibrosis: Pathogenesis and Management. Respiratory Research, Italy, v. 19, n. 1, p. 32, Feb. 2019. Available at: https://doi.org/doi.org/10.1186/s12931-018-0730-2

[33] SHAO, S. et al. Pharmacological expansion of type 2 alveolar epithelial cells promotes regenerative lower airway repair. Proc Natl Academy Sci USA, v. 121, n. 6, p. 2400077121, April/2024. Available at: https://doi.org/10.1073/pnas.2400077121

[34] SILVA et al. Challenges and Perspectives in the Management of Idiopathic Pulmonary Fibrosis: Towards More Effective Therapies. Ibero-America Magazine of Humanities and Science Education, Brazil, v. 10, n. 4, p. 1153-1160, April/2024. Available at:) https://doi.org/doi.org/10.51891/rease. v10i4.13558

[35] SIMON, K. S. *et al*. Innovative Pre-Clinical Data Using Peptides to Intervene in the Evolution of Pulmonary Fibrosis. Int J Mol Sci, Brazil, v. 24, n. 13, p. 11049, July/2023. Available at: https://doi.org/10.3390/ijms241311049

[36] SOFIA, C. et al. Promising advances in treatments for the management of idiopathic pulmonary fibrosis. Expert Opin Pharmacother, Italy, v. 25, n. 6, p. 717-725, April/2024. Available at: https://doi.org/10.1080/14656566.2024.2354460

[37] SOUZA, R. L. D; FRANCO, L. G. M. D. M; SIQUEIRA, M. C. D. General Approach to Idiopathic Pulmonary Fibrosis, Brazil, v. 23, n. 3, p. 1-7, March/2023. Available at: https://doi.org/10.25248/REAMed.e12623.2023 (Accessed on: 5 Aug. 2024).

[38] STELLA, G. M. et al. The oncogenic landscape of the idiopathic pulmonary fibrosis: a narrative review. Trans Lung Cancer Res, Italy, v. 11, n. 3, p. 472-496, March. /2022. Available at: https://doi.org/10.21037/tlcr-21-880

[39] SYNAPSE - Idiopathic Pulmonary Fibrosis: Current Clinical Research Status Targeting GPCR. Available at: https://synapse.patsnap.com/blog/idiopathic-pulmonary-fibrosis-current-clinical-research-status-targeting-gpcr (Accessed on: 6 Sept. 2024).

[40] TIRELLI, C. *et al*. The Genetic and Epigenetic Footprint in Idiopathic Pulmonary Fibrosis and Familial Pulmonary Fibrosis: A State-of-the-Art Review. Diagnostics (Basel), Italy, v. 12, n. 12, p. 3107, Dec./2022) https://doi.org/10.3390/diagnostics12123107

[41] TOMOS, I. *et al*. Molecular and Genetic Biomarkers in Idiopathic Pulmonary Fibrosis: Where Are We Now? Biomedicines, Greece v. 11, n. 10, p. 2796, Oct./2023. Available at: https://doi.org/10.3390/biomedicines11102796

[42] VOLKMANN, E. R. et al. Lysophosphatidic acid receptor 1 inhibition: a potential treatment target for pulmonary fibrosis. Eur Respir Rev, USA, v. 33, n. 172, p. 240015, June/2024. Available at: https://doi.org/10.1183/16000617.0015-2024

[43] YANG, S. *et al*. Therapeutic Applications of Mesenchymal Stem Cells in Idiopathic Pulmonary Fibrosis. Front Cell Dev Biol, China, v. 9, n. 9, p. 639657, March/2021. Available at: https://doi.org/10.3389/fcell.2021.639657

[44] YANG, Y. et al. Mesenchymal stem cells and pulmonary fibrosis: a bibliometric and visualization analysis of literature published between 2002 and 2021. Frontiers, China, v. 4, n. 1, p. 1, July/2023. Available at: https://doi.org/10.3389/fphar.2023. 1136761

[45] YOSHIHARA, M. *et al*. Administration of Collagen Peptide Prevents the Progression of Pulmonary Fibrosis in Bleomycin-Treated Mice. Biologics, Japan, v. 3, n. 3, p. 187-197, July/2023. Available at: https://doi.org/10.3390/biologics3030010 (Accessed on: 6 Jan. 2025).