Idiopathic Pulmonary Fibrosis

Thomas Koudstaal , Marlies S. Wijsenbeek

PII: S0755-4982(23)00003-9
DOI: https://doi.org/10.1016/j.lpm.2023.104166
Reference: LPM 104166

To appear in: *La Presse Médicale*

Please cite this article as: Thomas Koudstaal , Marlies S. Wijsenbeek , Idiopathic Pulmonary Fibrosis, *La Presse Médicale* (2023), doi: https://doi.org/10.1016/j.lpm.2023.104166

Idiopathic Pulmonary Fibrosis.

Thomas Koudstaal[1] M.D. PhD, Marlies S. Wijsenbeek[1] M.D. PhD

[1] *Center for Interstitial Lung Diseases and Sarcoidosis, Department of Pulmonary Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands.*

Abstract

Idiopathic pulmonary fibrosis (IPF) is a progressive devastating lung disease with substantial morbidity. It is associated with cough, dyspnea and impaired quality of life. If left untreated, IPF has a median survival of 3 years.

IPF affects ~3 million people worldwide, with increasing incidence in older patients. The current concept of pathogenesis is that pulmonary fibrosis results from repetitive injury to the lung epithelium, with fibroblast accumulation, myofibroblast activation, and deposition of matrix. These injuries, in combination with innate and adaptive immune responses, dysregulated wound repair and fibroblast dysfunction, lead to recurring tissue remodeling and self-perpetuating fibrosis as seen in IPF.

The diagnostic approach includes the exclusion of other interstitial lung diseases or underlying conditions and depends on a multidisciplinary team-based discussion combining radiological and clinical features and well as in some cases histology. In the last decade, considerable progress has been made in the understanding of IPF clinical management, with the availability of two drugs, pirfenidone and nintedanib, that decrease pulmonary lung function decline. However, current IPF therapies only slow disease progression and prognosis remains poor. Fortunately, there are multiple clinical trials ongoing with potential new therapies targeting different disease pathways.

This review provides an overview of IPF epidemiology, current insights in pathophysiology, diagnostic and therapeutic management approaches. Finally, a detailed description of current and evolving therapeutic approaches is also provided.

Key words:

Idiopathic Pulmonary Fibrosis, genetics, inflammation and immunity, therapeutic management

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic and progressive fibrotic lung disease characterized by progressive lung scarring in the interstitium of the lungs (1). This devastating disease is associated with increasing cough (2), dyspnea (1, 3), and has a detrimental effect on a patient's quality of life (QoL) as well as on life expectancy, with a median survival of 3 years when left untreated (4-6).

Diagnosis is based on the combination of clinical and radiological features, with only in a few occasions the need for histology. IPF is defined by the presence of a radiographic and/or histopathological pattern of (probable) usual interstitial pneumonia (UIP) in the absence of an alternative etiology for this pattern.

Current IPF therapies slow disease progression, but don't cure the disease. Lung transplantation (LungTX) is an option only for a small subgroup of patients and most patients primarily rely on antifibrotic therapy plus supportive and palliative measures.

For many years, IPF was considered a primarily inflammatory driven disease, considering the increase in inflammatory cells in IPF lungs. Several negative clinical trials (7) and even a harmful trial (8) for immunosuppressive drugs have sparked the debate whether the enhanced presence of immune cells locally might rather be an epiphenomenon than a primary driver of the disease. Recent exciting studies have led to the discovery of other important key players and pathways. The currently favored concept of pathogenesis proposes that IPF is characterized by epithelial involvement leading to increased production of fibroblast migration mediators, proliferation and differentiation into active myofibroblasts. Consequently, this will lead to secretion of exaggerated amounts of extracellular matrix (ECM) by myofibroblast, ultimately causing remodeling of the pulmonary architecture.

This review provides a comprehensive view of IPF epidemiology, current insights in pathophysiology, diagnostic and therapeutic management approaches. Finally, a detailed description of evolving therapeutic approaches is also provided.

2. Epidemiology

Determination of epidemiology in IPF is a substantial challenge. Owing to diagnostic challenges, updated diagnostic criteria, and differences in study methodologies there is substantial heterogeneity between studies providing estimated epidemiology data in IPF (1, 9). In a recent meta-analysis, Maher *et al* found incidence estimates (per 10,000 of the population) ranged from 0.35 to 1.30 in Asia–Pacific countries, 0.09 to 0.49 in Europe, and 0.75 to 0.93 in North America (9). Furthermore, adjusted prevalence estimates ranged from 0.57 to 4.51 in Asia–Pacific countries, 0.33 to 2.51 in Europe, and 2.40 to 2.98 in North America (9). Overall, IPF affects ∼3 million people worldwide, with substantial increase of incidence with age (10).

3. Pathophysiology

Although IPF pathogenesis remains elusive and most likely multifactorial in etiology, many recent advances have been made in unraveling the underlying driving mechanisms **(Figure 1)**. Histologically, IPF is characterized by excessive deposition of proteins of the extracellular matrix (ECM), the presence of fibroblast foci, and areas of fibrosis adjacent to areas of normal lung parenchyma. (11, 12). In IPF, numerous risk factors have been identified, including environmental exposures, smoking, chronic viral infections and certain comorbidities. In the past 5 years, many advances have also been made in determination of genetic risk factors. Genetic variants are estimated to explain up to one-third of the inherent individual risk of disease (13). In IPF, the natural process of cellular and molecular ageing is exaggerated and occurs prematurely. Alveolar epithelial cells, mainly alveolar epithelial type 2 cells (AT2s), are primarily affected. The complexity of IPF is also determined by an extensive number of multidirectional interactions between epithelial cells, mesenchymal cells and the ECM. However, the exact mechanisms of how these factors interact to cause disease remains largely unclear.

This section will cover in detail the current evidence on the contribution of these factors to IPF pathogenesis.

3.1 Genetics

To date, genome-wide association studies (14-19) (GWAS) have reported various common variant signals associated with IPF, stressing the importance of cell proliferation, host defense, lung development, inflammatory processes or cell-cell adhesion. The most intensely associated variant, rs35705950, in one of these signals that maps to the promoter region of the *MUC5B* gene has a much larger effect on disease susceptibility than other reported risk variants with each copy of the risk allele associated with a fivefold increase in odds of disease (20). However, in IPF patients on antifibrotic treatment, carriage of the *MUC5B* rs35705950 T allele was associated with longer survival (21). *MUC5B* plays an important part in mucociliary clearance and host defense, but the mechanisms for its involvement in IPF remain uncertain. This variant rs35705950 has a risk allele frequency of 35% in cases (compared with 11% in the general population) and so does not explain all IPF risk.

Rare variants in telomere-related and surfactant genes have also been implicated in familial pulmonary fibrosis (FPF) and sporadic IPF (22, 23). Variants in *TOLLIP* (encoding an inhibitor of the transforming growth factor-β (TGFβ) pathway and regulator innate immune responses) and *OBFC1* (encoding oligonucleotide/oligosaccharide-binding fold-containing 1; also known as STN1) as well as *TERC* and *TERT* have also been implicated in sporadic IPF. In the current guidelines, genetic testing for these variants is recommended in selected patients with idiopathic interstitial pneumonias (24).

In a recent GWAS meta-analysis, three novel regions were identified implicating the genes DEPTOR, KIF15 and MAD1L1 of the genome identified with IPF risk, supporting recent research showing mTOR signaling promotes lung fibrogenesis and also implicating spindle-assembly genes in the development of IPF (25).

Taken together, IPF development and progression is increasingly associated with genetic susceptibility leading to dysregulated host defense, telomere maintenance, cell–cell adhesion, and signaling with respect to disease susceptibility. Identifying these crucial regions of the genome contributing to disease risk will lead to improved understanding of the biological processes underlying IPF and helps in the development of novel therapeutic drug treatments (26).

3.2 Environmental factors

One of the defining features of IPF is the lack of a clear etiology. Diagnostic criteria in current guidelines advise the exclusion of secondary causes of ILD, including environmental exposures, connective tissue disease (CTD) and drug toxicity (1). Numerous studies have shown an association of environmental risk factors to IPF development, including viral infections, micro aspiration, tobacco smoke, air pollution and occupational exposures (27). One intrinsic environmental factor, gastro-esophageal reflux disease (GERD), is a well-known comorbidity in individuals with IPF and has been proposed as a cause of disease development and progression (28, 29). Interestingly, some studies reported survival benefits for patients with IPF who were receiving antacid therapy (30, 31). However, In the latest update, current guidelines based on the latest studies advise against the use of antacid therapy to treat IPF (1).

Another important risk factor is the lung microbiota, including bacteria, fungi, viruses and bacteriophages, and has also become an interesting field of scientific interest and has led to important studies regarding therapeutic interventions. Bacteria and viruses are known for causing direct airway epithelial cells injury and indirect damage by activation of host immune responses after infection (32). The crucial importance of a well-functioning host defense was suggested in the PANTHER-IPF (Prednisone, Azathioprine, and *N*-acetylcysteine: a Study that Evaluates Response in IPF) study, which showed worse outcomes in patients with IPF who were treated with a combination of immunosuppressive drugs (33).

Studies provided evidence for an altered microbiome with higher bacterial burden in IPF. The etiology of these changes to the microbial environment is unknown, but might be caused by recurrent gut micro aspiration or a defective immune defense, or a consequence of the distorted parenchymal architecture from fibrosis (32). However, in a recent study among adults with idiopathic pulmonary fibrosis, the addition of co-trimoxazole or doxycycline to usual care, compared with usual care alone, did not significantly improve time to nonelective respiratory hospitalization or death (34, 35). This demonstrates the complex nature of IPF pathobiology in which a single intervention to environmental factors might not be sufficient to alter the disease development and

outcome. Viral infections, especially the human herpes virus and the adenovirus, are suggested to be involved as either exacerbating agents or initiators of disease. An increased incidence of human herpes viruses, such as cytomegalovirus, is seen in the lung samples of patients with IPF, acute IPF exacerbations and asymptomatic individuals who are at risk for familial IPF (36).

Taken together, occult intrinsic and extrinsic environmental factors affect the lung microenvironment and may contribute to the development and progression of IPF.

3.3 Epithelial cells, myofibroblasts and the immune system

Alveolar epithelial cells, mainly alveolar epithelial type 2 cells (AT2s), are primarily affected in IPF pathogenesis. AT2s secrete surfactant and have crucial metabolic and immunological functions and are progenitor cells for alveolar epithelial type 1 cells (AT1s), which are known for maintaining alveolar epithelial turnover. In IPF, AT2s demonstrate genomic instability, telomere attrition, epigenetic changes, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence and altered intercellular communication (37). A leading concept is that AT2 depletion through repetitive micro-injuries could be the underlying cause of lung fibrosis (38). Indeed, targeted deletion of AT2 cells is sufficient to induce a fibrotic response in the lungs, but it is not sustained (39, 40). Additional data supporting this idea of stem cell exhaustion is that the number of AT2 cells are diminished in IPF lungs (41, 42). However, the depletion of this vital progenitor cell is not only a function of the distorted lung architecture but may also be a precursor to fibrosis [39]. Since the advent of single-cell RNA sequencing (scRNA-Seq), several studies in the past five years have revolutionized the concept of epithelial cell populations in IPF. Over time, scRNA-seq studies identified up to 10 distinct clusters of epithelial cells. Although all studies identified most classical epithelial cell types, i.e., AT1s, AT2s, basal, ciliated, and secretory cells by similar expression signatures, there are some differences in subcategorization of the described cell type clusters (43).

Another key effector cell, the myofibroblast, is a central mediator of fibrotic diseases, including IPF. In response to injury, fibroblasts migrate to the site of damage and differentiate into myofibroblasts. in IPF, interstitial fibroblasts and myofibroblasts organize in lesions known as fibroblastic foci (FF). Myofibroblasts are thought to be responsible for synthesizing extracellular matrix (ECM) components via a TGF-b–dependent mechanism (44). In the wound healing process, myofibroblasts undergo apoptosis and re-epithelialization occurs (45-47). Conversely, myofibroblast accumulation and impaired re-epithelialization are the pathologic hallmarks of fibrotic disease (48-50). Persistent myofibroblast activation/accumulation in injured tissues and the inability to terminate host reparative functions, may be responsible for the progressive nature of fibrotic diseases such as IPF (51, 52). Accumulating studies support the concept that senescence may promote profibrotic effects via impaired myofibroblast dedifferentiation and apoptosis resistance, which contributes to myofibroblast accumulation and ultimately persistent fibrosis in aging (53). This might suggest that targeting myofibroblast dedifferentiation or apoptotic clearance of senescent cells may be more effective than strategies that block fibrosis development (54).

Although the exact etiology in IPF is unknown and probably diverse, all stages of fibrosis are accompanied by innate and adaptive immune responses. New insights have provided further evidence that innate and adaptive immune system are involved during the development of fibrosis (7).

Innate immunity is our swift first-line defense against microorganisms and foreign pathogens, which is very broad and nonspecific. Innate immune responses are usually initiated and executed by macrophages, neutrophils, natural killer (NK) cells and dendritic cells (DCs). Recruitment and differentiation of monocytes is driven by the surrounding microenvironment, with circulating monocytes having the potential to become interstitial or airway macrophages or dendritic cells (35-38). Strikingly, elevated monocyte count was associated with increased risks of IPF progression, hospitalization, and mortality (55). Over the past decade, macrophage have also been recognized to play a significant role in IPF pathogenesis. Macrophages are known for their central role in tissue repair and immunity. Two subsets exist; activated (M1) macrophages and alternatively activated (M2) macrophages. In IPF, macrophages, dependant of the local cytokine environment, may exhibit anti-fibrotic, pro-fibrotic and tissue-regenerating functions. M2 macrophages appear to play a crucial role in regulation of fibrosis (56) and could even be involved in acute exacerbations of IPF (AE-IPF) (57).

In parallel to activation of our innate immune system, adaptive immune responses are initiated, which allows for more specific responses executed by T and B lymphocytes. T-cells have been identified in active-disease regions and tertiary lymphoid organs (TLOs) in lungs and BAL of patients with IPF (58-61). Over the past decade, evidence has been found for the involvement of several T helper subsets, such as Th1, Th2, Th9 and Th17 cells. However, the potential mechanism of pathologic involvement of T cells in the IPF lung parenchyma remains uncertain and T cells may have both negative and positive roles. Indeed, previous studies have some subsets of T cells in the lung might be protective, whereas others accelerate disease progression (62). B cells represent another arm of the adaptive immune system. In IPF, increased numbers of B-cells are found in the lung of IPF patients (58, 60). Further evidence for B cell involvement was provided with enhanced levels of a B lymphocyte stimulator, which is also known as B-cell-activating factor (BAFF), in the lungs and blood of patients with IPF (63).

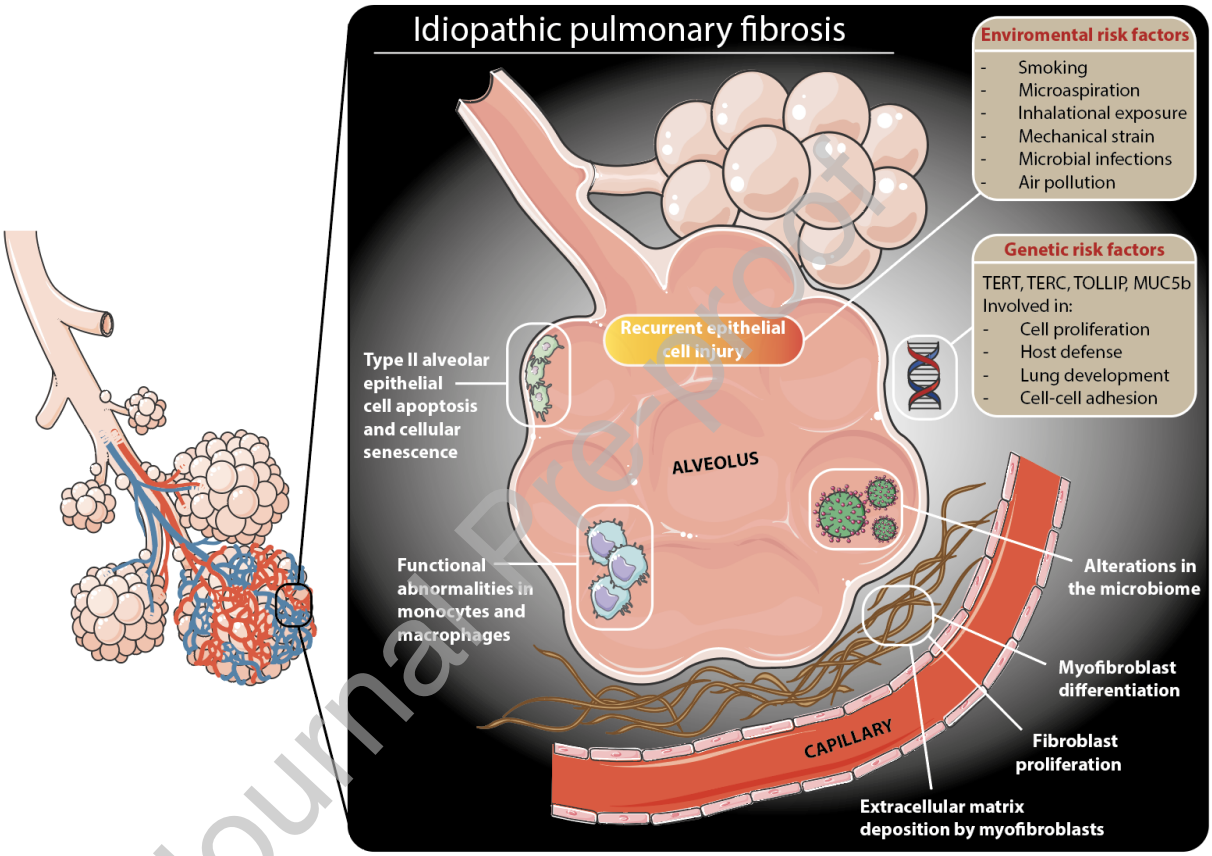

Figure 1. Schematic overview of current insights in IPF pathogenesis.

4. Diagnostic and therapeutical management

4.1 Diagnosis

Diagnostic delay is unfortunately common in IPF, considering that a median length in time was reported to be between 0.6 and 2.3 years from onset of symptoms until a final diagnosis was made (64-70). A recent study demonstrated that a diagnostic delay of more than 1year negatively impacts progression-free survival, quality of life and hospitalisation rates in patients with IPF, highlighting the importance of an early diagnosis for proper management of IPF (71).

When interstitial lung disease is suspected in a patient, a focused history taking and physical examination should be performed to identify disorders that can present in a similar way as IPF, such as chronic hypersensitivity pneumonitis or connective-tissue diseases. Patients should be meticulously questioned about domestic and work exposures, medication or other substance use as well as previous medical history, family history and complaint of extra pulmonary disease. Physical examination may reveal signs of CTD, early aging, clubbing and

crepitations on auscultation of the lungs. Guidelines also recommend serological testing to exclude connective tissue diseases. It is generally accepted to include at least testing for antinuclear antibodies; rheumatoid factor; anti–cyclic citrullinated peptide antibodies; antibodies against Scl-70, SS-A, and Jo-1. In selected cases, a more extensive panel of anti-synthetase antibodies, systemic sclerosis panel and myositis antibodies should be considered according to the guidelines (10). Input from an immunologist or rheumatologist should be considered when the history, physical examination, or serologic testing suggests autoimmune disease.

high-resolution CT scan of the chest is mandated in the work-up of IPF and other interstitial lung diseases (1). In IPF, the term UIP is used to describe a high-resolution CT pattern characterized (**Figure 2**). A "definite UIP" pattern is characterized by bilateral reticulation and honeycombing that is predominantly peripheral and in the lower lobes. A "probable UIP" pattern is defined as bilateral reticulation that is predominantly peripheral and in the lower lobes, with traction bronchiectasis but without honeycombing can also suggestive of an underlying histologic UIP pattern (72) and can be sufficient for the diagnosis of IPF in the current guidelines (1). Lastly, an "indeterminate" UIP pattern, consists of atypical features on high-resolution CT such as upper-lung or midlung predominance, peri-bronchovascular predominance, subpleural sparing predominant consolidation, extensive ground-glass opacities, extensive mosaic attenuation, and diffuse nodules or cysts, and should raise suspicion of an interstitial lung disease other than IPF (72).

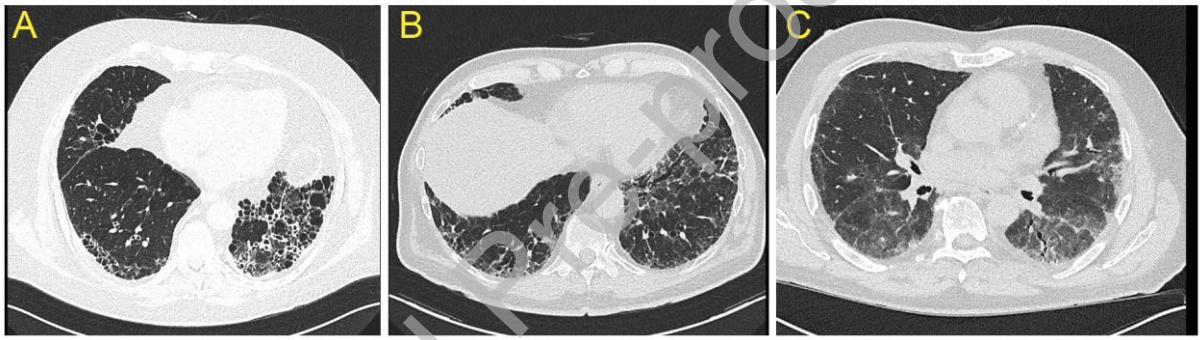

Figure 2. High-resolution computed tomography (CT) images demonstrating a definite (A), probable (B), and indeterminate (C) usual interstitial pneumonia pattern (UIP).

Identifying these different patterns can be difficult, and referral to a ILD expertise center could help establish an accurate diagnosis without a lung biopsy. When the combination of clinical and imaging data is not diagnostic, a thoracoscopic lung biopsy or transbronchial lung cryobiopsy (TLBC) can be considered if the results are expected to influence therapy. It is important to always discuss the risks – consequence balance with patients .The procedure should not be performed in high-risk patients, including those with high oxygen requirements (e.g., >2 liters per minute), pulmonary hypertension, rapid disease progression, severely reduced FVC or DLCO, multiple coexisting conditions, or frailty (73). Transbronchial lung cryobiopsy may be preferred to surgical lung biopsy (SLB) in centers with appropriate expertise and/or in some patient populations (74). The diagnostic yield of TBLC in patients with ILD of undetermined type was 79% (1). In TBLC, pooled incidences of complications were 9.9% (95% CI 6.8–14.3) for significant bleeding (6.9% for centres with ≥70 TBLC), 5.6% (95% CI 3.8–8.2) for pneumothorax treated with a chest tube and 1.4% (95% CI 0.9–2.2) for acute exacerbation of ILD after TBLC. The mortality rates were 0.6% and 1.7% for TBLC and VATS, respectively (75). Further advances have also been made in this field, with development of a gene-expression signature developed to enhance the identification of a UIP pattern (1); this approach has been extended to transbronchial lung-biopsy samples (76). Currently, it remains unclear how such molecular approaches will be integrated into clinical practice (1).

Multi-disciplinary team discussion is currently considered the "gold standard" in the diagnosis of IPF, though even in that setting a subgroup of patients will remain unclassified (U-ILD).

4.2 non-pharmacological management

Nonpharmacologic management strategies are equally important as pharmacological interventions and can profoundly aid IPF patients to cope with their disease and strive to maintain quality of life for as long as possible. Smoking cessation should be a priority for patients who are actively using tobacco products. Moreover, current guidelines suggest that Influenza, pneumococcal, and other age-appropriate vaccines should be administered.

Supplemental oxygen
Clinical practice guidelines recommend supplemental oxygen for patients with IPF (77). Oxygen administration has shown to reduce exertional dyspnea and improve exercise tolerance (78). An oxyhemoglobin saturation of 88% or less at rest, 6-minute walk tests or treadmill testing, or during sleep should prompt discussion with the patient about initiation of (ambulatory) oxygen therapy.

Pulmonary rehabilitation
Pulmonary rehabilitation, a structured exercise program designed for adults with advanced lung disease, has been shown to improve exercise capacity and health-related quality of life for patients with IPF (79, 80). However, long-term effect often weans out, though nowadays continued support via digital solutions may help improve maintaining training effects. Timely referral to pulmonary rehabilitation programs is associated with more yield of the programme (81).

Advanced Care planning.
Advance care planning (ACP) is the ongoing communication process for patients to determine their expectancies and preferences for medical care, and to discuss them with family and health care providers. Lack of ACP discussions are a known patient-clinician communication gap in IPF (82). Identified barriers are health care professional (HCP) reluctance, an unpredictable disease trajectory, insufficient communication training, prioritization, and patient readiness (83). Another challenge is that timely initiation of palliative care is often lacking. Interestingly, the surprise question "Would you be surprised if this patient died within the next year?" was shown to be an accurate predictor of 1-year mortality in IPF (84). This relatively simple tool could enable more timely focus on palliative care for patients with IPF.

Lung transplantation
Over 4600 lung transplantations are performed worldwide each year, approximately half of which are performed for interstitial lung disease (85). Lung transplantation (LungTx) can be a life-extending treatment option for patients with advanced and/or progressive fibrotic interstitial lung disease (ILD), including idiopathic pulmonary fibrosis (IPF) (86). IPF is now the most common indication for LungTx worldwide. In appropriate cases, IPF disease progression should prompt early referral to a LungTx centre concurrent with care at an ILD centre to guide slowing the fibrotic lung disease, stabilising overall clinical status and optimising a candidate for LungTx (87).

4.3 Current pharmacological management

Over the last decade, considerable advances have been made in pharmacotherapeutic approaches to IPF (1), (Figure 3). Two antifibrotic drugs, nintedanib and pirfenidone, are safe and efficacious in IPF treatment and are recommended in current guidelines for use in patients with IPF (1). In placebo-controlled, randomized trials, each drug has shown an approximate 50% reduction in the rate of FVC decline over the course of 1 year (88, 89). Both have shown some efficacy in reducing severe respiratory events, such as acute exacerbations, and hospitalization for respiratory events (90, 91). Furthermore, subsequent meta-analyses suggest that these agents also reduce mortality (92, 93).

Nintedanib is a tyrosine kinase inhibitor that targets growth factor pathways such as vascular endothelial growth factor receptors 1, 2, and 3, fibroblast growth factor receptors 1, 2, and 3, and platelet-

derived growth factor receptor (94-96). Patients should initially be prescribed an oral dose of 150 mg twice daily of nintedanib. The most reported side effect is diarrhea, which can often be managed with antidiarrheal agents (89). The dose can be decreased to 100 mg twice daily if unmanageable side effects occur. Historically, some cases of drug-induced liver injury have been reported. Therefore, close monitoring of liver function should be tested at baseline, monthly for the first 3 months, and then monitored as clinically indicated. Considering that nintedanib is associated with a small increase in the risk of bleeding, this drug should be used cautiously in patients receiving a therapeutic dosage of anticoagulant therapy.

Pirfenidone has a number of anti-inflammatory and antifibrotic effects, including inhibition of collagen synthesis, down-regulation of TGF-β and tumor necrosis factor alpha, and a reduction in fibroblast proliferation (97). Pirfenidone is prescribed in an escalating-dose fashion over a 14-day period: 267 mg (one capsule) by mouth three times daily for 1 week, 534 mg (two capsules) three times daily for 1 week, and 801 mg (three capsules) three times daily thereafter. Patients can subsequently be transitioned to an 801-mg tablet three times daily. Well-known side effects, such as anorexia, nausea, and vomiting (88), can often be successfully treated with antacids and antiemetic agents. In some cases, side effects are severe enough to require a lower total daily dose (six to eight capsules daily). Caution is advised with exposure to sunlight, as a photosensitive rash can also occur during pirfenidon treatment. Similar to nintedanib, close monitoring of liver functions should be performed periodically.

It is difficult to recommend one agent over the other, since no head-to-head comparison and superiority trial is available. A network meta-analysis concluded that pirfenidone and nintedanib provide similar benefits (98, 99). Currently, no good data are available to guide clinicians regarding how a response should be defined, and when the therapy should be discontinued. Factors as tolerability, quality of life and life expectancy should weigh in when discussing treatment decisions with patients. (100). In clinical practice, regular follow-up (3-6 months) and assessing tolerability and lung function are recommended (1).

4.4. Potential novel IPF therapies

Significant advances in understanding IPF pathobiology have led to exciting clinical trials with novel drugs, targeting different compartments/cells involved in the pathogenesis of IPF. Below we describe a selection of compounds that are currently investigated in phase two and three clinical trials, or have recently been terminated.

Extracellular matrix

4.4.1 Pamrevlumab

Pamvrevlumab is an intravenous human monoclonal antibody targeting connective tissue disease growth factor (CTGF). A phase 2 trial of pamrevlumab, showed a decreased decline in FVC, as compared with placebo, over a period of 48 weeks (101). Currently, these findings are being investigated in a Phase III clinical trial (NCT03955146).

4.4.2 Autotaxin inhibiters

Autotaxin (ATX) is the enzyme responsible for the production of extracellular lysophosphatidic acid (LPA). LPA1 has been implicated in the development of IPF, given its role in mediation of fibroblast recruitment, vascular leak, and endothelial barrier dysfunction in animal models. GLPG1690, a selective ATX inhibitor, reduced circulating LPA levels and influenced lung function and functional respiratory imaging findings in a 12-week, randomized placebo-controlled phase II clinical trial (NCT02738801). However, the parallel phase three studies ISABELA 1 and 2 were prematurely discontinued due to lack of efficacy and potential increased risks. (NCT03711162, NCT03733444). Related to this pathway, several ATX inhibitors have been discovered and are in early stage of clinical and pre-clinical development (102, 103). Most importantly, BMS-986,020, a lysophosphatidic acid receptor antagonist has been tested in a phase II clinical trial, which terminated early due to the development of cholecystitis in treated patients. Both regimens of BMS-986020 were associated with

elevations in hepatic enzymes. (NCT01766817), however, in the treatment period of 26 weeks BMS-986,020, there was a significant reduction in the rate of FVC decline (104).

4.4.3 TGF- β pathway

The transforming growth factor β (TGF β) is a well-studied cytokine involved in fibrotic processes.
Two drugs targeting the TGF β pathway are under evaluation in IPF. A phase II study with BG00011, a humanized subcutaneously administered monoclonal antibody that inhibits αvβ6, (NCT01371305**)** reached an early termination due unclarified safety concerns. An inhaled integrin αv antagonist GSK3008348, has been tested in healthy individuals in a Phase I trial and was well-tolerated (105) (NCT02612051). The drug was also tested in a limited number of IPF patients, in a pharmacokinetic/target engagement study using Positron Emission Tomography (PET) Imaging (NCT03069989).

4.4.4 Prostacyclin pathway

Treprostinil, a prostacyclin analogue, promotes vasodilation of pulmonary and systemic arterial vascular beds and has inhibitory effects on platelet aggregation. In addition to its effects on the pulmonary vasculature, there are data to suggest that Treprostinil has antifibrotic properties by interfering with fibroblast biology. In the INCREASE trial (106), pulmonary hypertension due to IPF (PH-ILD) patients received inhaled Treprostinil. A post-hoc analysis showed an increase in FVC from baseline versus FVC decline in placebo treated patients. A current phase III trial (TETON-1 and TETON-2) will investigate if these effects are also seen in IPF patients (107).

Targeting inflammation and immunity

Current treatment guidelines for IPF include a strong recommendation against the use of high dose immunosuppression. This is based on the results of Panther trial where prednisone in combination with azathioprine and oral *N*-acetylcysteine was associated with increased mortality (8). Although it is still common practice to use high dose of immune suppression in case of acute exacerbations of IPF(108), this practice is not supported by good evidence. Furthermore a recent French multicenter trial showed that cyclophosphamide for acute exacerbations of IPF was associated with increased mortality (109). Different retrospective studies also report on a potential harmful effect on the use of high dose immunosuppression in AE-IPF, underlining the importance for further clinical studies.

Antifibrotic therapies

4.4.5 Phosphodiesterase-4 pathway

Phosphodiesterase-4 (PDE4) is a key enzyme class which is responsible for the hydrolysis of cyclic adenosine monophosphate (cAMP). Phosphodiesterase 4 (PDE4) inhibition is associated with antifibrotic effects by restoration of apoptosis of myofibroblasts and anti-inflammatory properties (110, 111). In a 12-week phase 2 trial, BI1015550, an oral preferential inhibitor of the PDE4B subtype, completely prevented decrease in lung function in patients with idiopathic pulmonary fibrosis . Currently, a two parallel phase III trials are ongoing to further study BI1015550 both in IPF (NCT05321069) as well as in patients with progressive pulmonary fibrosis other than IPF (NCT05321082).

4.4.6 Recombinant Pentraxin 2

Pentraxin-2 (PTX-2) is a circulating plasma protein and a soluble pattern recognition receptor of the innate immune system, that regulates monocyte/macrophage differentiation, acting as an antifibrotic and anti-inflammatory agent (112). In a 28-week, phase II clinical trial recombinant human Pentraxin-2 exhibited safety was studies which showed no major adverse events (113) (NCT01371305) and was found to be effective in reducing the rate of FVC decline in IPF patients (NCT02550873) and results of the phase III trial (NCT04552899) are still awaited.

4.4.7 Galectin inhibitors

Cellular responses to TGF β are speculated to be altered by the Galectin protein family which are synthesized on free ribosomes in the cytosol and then relocated to the extracellular space. TD139 is an inhaled, dry powder targeting galectin-3 that has been tested in a phase 1b/2a clinical trial (NCT02257177). The study evaluated TD139 safety, tolerability, pharmacodynamics and pharmacokinetics in healthy volunteers and IPF patients. The drug was administered using an inhaler device testing 3 separate doses for 14 days. Drug effects were evaluated by measurement of galectin-3 expression in alveolar macrophages before and after therapy. The results suggest a good safety profile of the drug and galectin-3 suppression in alveolar macrophages post treatment. Currently, a Phase IIb trial is recruiting patients with IPF to test efficacy (114).

4.4.8 GPR84 inhibitor/GLPG1205

GPR84 is a fatty acid receptor expressed in immune cells and is involved in promoting chronic inflammation, considering its overexpressing during inflammation. Prior studies have linked GRP84 receptors to renal fibrosis, with amelioration after ablation (115). However, the PINTA trial (NCT03725852), studying the GPR84 inhibitor GLPG1205, was negative for its primary endpoint of FVC change from baseline.

4.4.9 JNK inhibitors

As a member of the mitogen activated kinase (MAP-kinases) family, C-Jun Nh2-terminal kinase (JNK) is involved in cell proliferation, differentiation and apoptosis. JNK inhibitor CC-930 was evaluated in a phase I/II study in healthy subjects and IPF patients and was found to be safe. Moreover, biomarkers related to fibrosis were found to be reduced in a dose dependent manner (116). CC-90,001, a second generation JNK inhibitor is currently under evaluation in a phase II trial (NCT03142191).

4.4.10 ROCK-2 inhibitors

Rho-associated coiled-coil–forming protein kinases (ROCK) 1 and 2 are downstream GTPases of multiple pathways involved in pulmonary fibrosis including LPA and TGF-β pathways (117). The KD025, selective ROCK2 inhibitor is currently under evaluation for the treatment of IPF in an ongoing phase 2 study (NCT02688647).

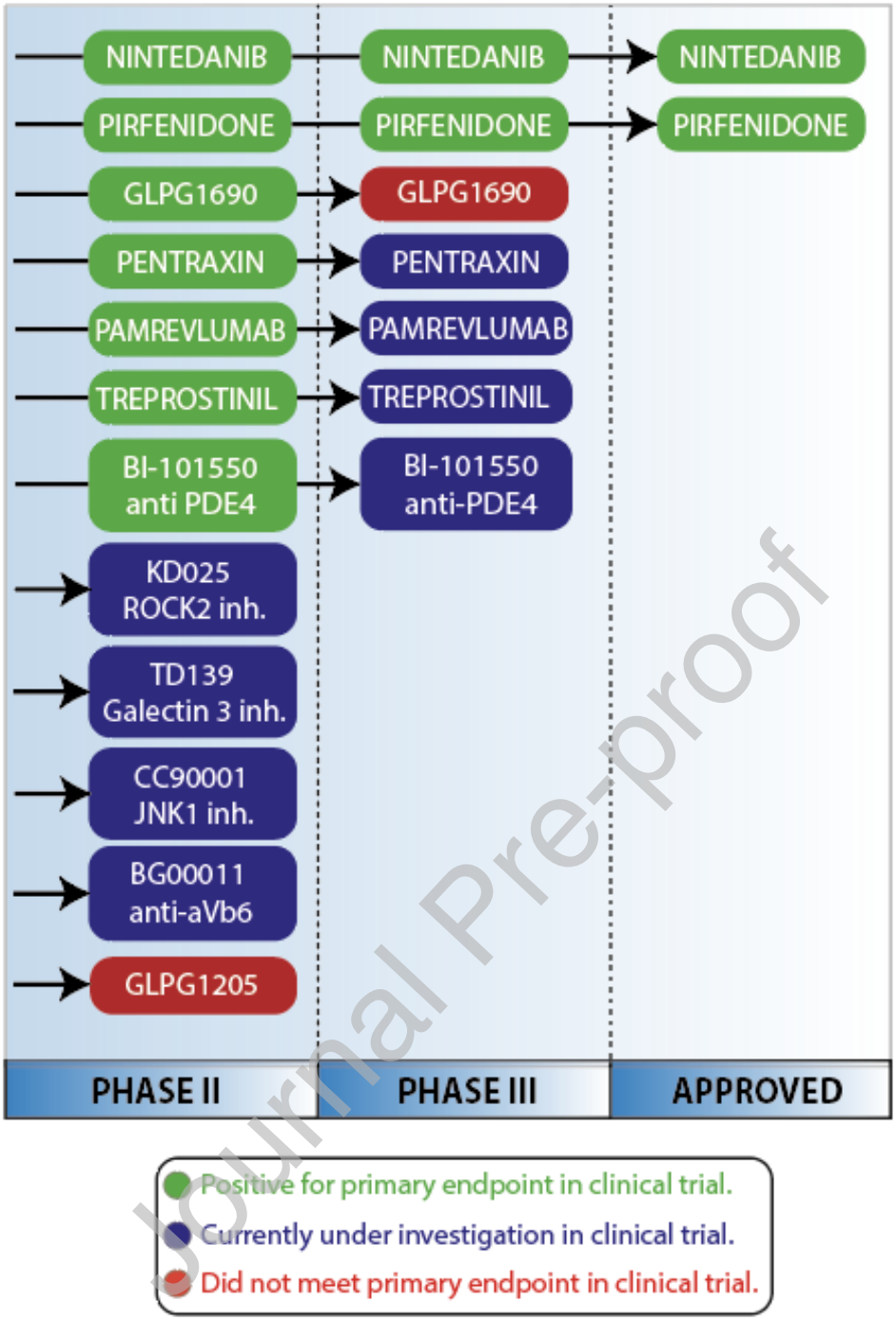

Figure 3. Schematic figure of the approved and most promising emerging drug targets for IPF treatment.

5. Future directions

Despite encouraging breakthroughs and advances that have been made in the last decade in the IPF field, prognosis remains poor and IPF is still characterized by a high burden of disease. Our understanding of IPF pathobiology is improving profoundly. Technologies such as large-scale single cell RNA sequencing and bioinformatics analysis will help identify new treatment targets and guide future drug development. Despite disappointing results from recent large phase three trials, several compounds are under investigation, hopefully leading to (combination) therapies that are more effective than current mono therapies , or even halt or reverse disease progression. Furthermore, techniques such as deep learning has been applied to HRCT imaging as well biomarkers with promising results to predict disease course (118). Such technique may help trial design by

including patients with more progressive disease. Whilst many of these technique and biomarkers are still in research setting, translation to clinical practice may help treatment decisions and evaluate response to therapy. it remains important that besides physiological outcome measures patient centered outcomes are structurally incorporated not only in clinical trials but also in daily care (119). Digital tools and wearables could provide means to more structurally assess patient's experiences, values and wishes to provide truly personalised care. recent studies in other forms of progressive pulmonary fibrosis have shown similar disease behaviour and response to therapy as in IPF (120), which opens the door to a management approach that is more based on communalities of disease behaviour and underlying pathobiology, than of diagnostic labelling. Where for now the diagnosis of IPF is still a separate entity (1), it could be envisioned that in future IPF no longer stays "idiopathic" , and patients will be grouped based on common features such as HRCT patterns, pathobiological factors or disease behaviour, or a combination of those (121).

As currently, there are no curative pharmacological treatments for patients with IPF, supportive care aimed at quality of life remains an area that deserves more attention. Equal access to diagnosis and care for all around the world affected by IPF is currently a dream, but healthcare providers should collaborate with patients, policymakers, pharmaceutical companies and other stakeholders to make progress in the care for all patients with IPF. Taken together, IPF is a rare uncurable disease characterized by a high burden of disease, with evolving encouraging unraveling of the underlying pathobiology, hopefully leading to novel therapeutic options in the future.

Author disclosures:

MSW reports grants from Boehringer Ingelheim, Hoffman la Roche, The Netherlands Organisation for Health Research and Development, The Dutch Lung Foundation, and The Dutch Pulmonary Fibrosis Foundation; consulting fees from Boehringer Ingelheim, Hoffman la Roche, Galapagos, Bristol Myers Squibb (BMS), Galecto, Respivant, Nerretherapeutics, PureTech Health, Kinevant Sciences, Molecure, Horizontherapeutics, and CSL Behring; speaker fees from Boehringer Ingelheim, Hoffman la Roche, and Novartis; support for attending meetings from Boehringer Ingelheim, Hoffman la Roche, and Galapagos;. All grant and fees were paid to her institution.

REFERENCES

1. Raghu G, Remy-Jardin M, Richeldi L, Thomson CC, Inoue Y, Johkoh T, et al. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med. 2022;205(9):e18-e47.
2. van Manen MJ, Birring SS, Vancheri C, Cottin V, Renzoni EA, Russell AM, et al. Cough in idiopathic pulmonary fibrosis. Eur Respir Rev. 2016;25(141):278-86.
3. Kim HJ, Perlman D, Tomic R. Natural history of idiopathic pulmonary fibrosis. Respir Med. 2015;109(6):661-70.
4. Cox IA, Borchers Arriagada N, de Graaff B, Corte TJ, Glaspole I, Lartey S, et al. Health-related quality of life of patients with idiopathic pulmonary fibrosis: a systematic review and meta-analysis. Eur Respir Rev. 2020;29(158).
5. van Manen MJ, Geelhoed JJ, Tak NC, Wijsenbeek MS. Optimizing quality of life in patients with idiopathic pulmonary fibrosis. Ther Adv Respir Dis. 2017;11(3):157-69.

6. Kreuter M, Swigris J, Pittrow D, Geier S, Klotsche J, Prasse A, et al. The clinical course of idiopathic pulmonary fibrosis and its association to quality of life over time: longitudinal data from the INSIGHTS-IPF registry. Respir Res. 2019;20(1):59.
7. Heukels P, Moor CC, von der Thusen JH, Wijsenbeek MS, Kool M. Inflammation and immunity in IPF pathogenesis and treatment. Respir Med. 2019;147:79-91.
8. Idiopathic Pulmonary Fibrosis Clinical Research N, Raghu G, Anstrom KJ, King TE, Jr., Lasky JA, Martinez FJ. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. N Engl J Med. 2012;366(21):1968-77.
9. Maher TM, Bendstrup E, Dron L, Langley J, Smith G, Khalid JM, et al. Global incidence and prevalence of idiopathic pulmonary fibrosis. Respir Res. 2021;22(1):197.
10. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, et al. Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med. 2018;198(5):e44-e68.
11. Fernandez IE, Eickelberg O. New cellular and molecular mechanisms of lung injury and fibrosis in idiopathic pulmonary fibrosis. Lancet. 2012;380(9842):680-8.
12. Wynn TA. Integrating mechanisms of pulmonary fibrosis. J Exp Med. 2011;208(7):1339-50.
13. Mathai SK, Newton CA, Schwartz DA, Garcia CK. Pulmonary fibrosis in the era of stratified medicine. Thorax. 2016;71(12):1154-60.
14. Mushiroda T, Wattanapokayakit S, Takahashi A, Nukiwa T, Kudoh S, Ogura T, et al. A genome-wide association study identifies an association of a common variant in TERT with susceptibility to idiopathic pulmonary fibrosis. J Med Genet. 2008;45(10):654-6.
15. Noth I, Zhang Y, Ma SF, Flores C, Barber M, Huang Y, et al. Genetic variants associated with idiopathic pulmonary fibrosis susceptibility and mortality: a genome-wide association study. Lancet Respir Med. 2013;1(4):309-17.
16. Fingerlin TE, Murphy E, Zhang W, Peljto AL, Brown KK, Steele MP, et al. Genome-wide association study identifies multiple susceptibility loci for pulmonary fibrosis. Nat Genet. 2013;45(6):613-20.
17. Fingerlin TE, Zhang W, Yang IV, Ainsworth HC, Russell PH, Blumhagen RZ, et al. Genome-wide imputation study identifies novel HLA locus for pulmonary fibrosis and potential role for auto-immunity in fibrotic idiopathic interstitial pneumonia. BMC Genet. 2016;17(1):74.
18. Allen RJ, Porte J, Braybrooke R, Flores C, Fingerlin TE, Oldham JM, et al. Genetic variants associated with susceptibility to idiopathic pulmonary fibrosis in people of European ancestry: a genome-wide association study. Lancet Respir Med. 2017;5(11):869-80.
19. Peljto AL, Blumhagen RZ, Walts AD, Cardwell J, Powers J, Corte TJ, et al. Idiopathic Pulmonary Fibrosis Is Associated with Common Genetic Variants and Limited Rare Variants. Am J Respir Crit Care Med. 2023.
20. Zhu QQ, Zhang XL, Zhang SM, Tang SW, Min HY, Yi L, et al. Association Between the MUC5B Promoter Polymorphism rs35705950 and Idiopathic Pulmonary Fibrosis: A Meta-analysis and Trial Sequential Analysis in Caucasian and Asian Populations. Medicine (Baltimore). 2015;94(43):e1901.
21. Biondini D, Cocconcelli E, Bernardinello N, Lorenzoni G, Rigobello C, Lococo S, et al. Prognostic role of MUC5B rs35705950 genotype in patients with idiopathic pulmonary fibrosis (IPF) on antifibrotic treatment. Respir Res. 2021;22(1):98.

22. Coghlan MA, Shifren A, Huang HJ, Russell TD, Mitra RD, Zhang Q, et al. Sequencing of idiopathic pulmonary fibrosis-related genes reveals independent single gene associations. BMJ Open Respir Res. 2014;1(1):e000057.
23. Petrovski S, Todd JL, Durheim MT, Wang Q, Chien JW, Kelly FL, et al. An Exome Sequencing Study to Assess the Role of Rare Genetic Variation in Pulmonary Fibrosis. Am J Respir Crit Care Med. 2017;196(1):82-93.
24. Kropski JA, Young LR, Cogan JD, Mitchell DB, Lancaster LH, Worrell JA, et al. Genetic Evaluation and Testing of Patients and Families with Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med. 2017;195(11):1423-8.
25. Allen RJ, Guillen-Guio B, Oldham JM, Ma SF, Dressen A, Paynton ML, et al. Genome-Wide Association Study of Susceptibility to Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med. 2020;201(5):564-74.
26. Nelson MR, Tipney H, Painter JL, Shen J, Nicoletti P, Shen Y, et al. The support of human genetic evidence for approved drug indications. Nat Genet. 2015;47(8):856-60.
27. Sack C, Raghu G. Idiopathic pulmonary fibrosis: unmasking cryptogenic environmental factors. Eur Respir J. 2019;53(2).
28. Raghu G, Meyer KC. Silent gastro-oesophageal reflux and microaspiration in IPF: mounting evidence for anti-reflux therapy? Eur Respir J. 2012;39(2):242-5.
29. Ghebre YT, Raghu G. Idiopathic Pulmonary Fibrosis: Novel Concepts of Proton Pump Inhibitors as Antifibrotic Drugs. Am J Respir Crit Care Med. 2016;193(12):1345-52.
30. Lee JS, Collard HR, Anstrom KJ, Martinez FJ, Noth I, Roberts RS, et al. Anti-acid treatment and disease progression in idiopathic pulmonary fibrosis: an analysis of data from three randomised controlled trials. Lancet Respir Med. 2013;1(5):369-76.
31. Lee JS, Ryu JH, Elicker BM, Lydell CP, Jones KD, Wolters PJ, et al. Gastroesophageal reflux therapy is associated with longer survival in patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2011;184(12):1390-4.
32. Fastres A, Felice F, Roels E, Moermans C, Corhay JL, Bureau F, et al. The Lung Microbiome in Idiopathic Pulmonary Fibrosis: A Promising Approach for Targeted Therapies. Int J Mol Sci. 2017;18(12).
33. Moore BB, Moore TA. Viruses in Idiopathic Pulmonary Fibrosis. Etiology and Exacerbation. Ann Am Thorac Soc. 2015;12 Suppl 2(Suppl 2):S186-92.
34. Martinez FJ, Yow E, Flaherty KR, Snyder LD, Durheim MT, Wisniewski SR, et al. Effect of Antimicrobial Therapy on Respiratory Hospitalization or Death in Adults With Idiopathic Pulmonary Fibrosis: The CleanUP-IPF Randomized Clinical Trial. JAMA. 2021;325(18):1841-51.
35. Wilson AM, Clark AB, Cahn T, Chilvers ER, Fraser W, Hammond M, et al. Effect of Co-trimoxazole (Trimethoprim-Sulfamethoxazole) vs Placebo on Death, Lung Transplant, or Hospital Admission in Patients With Moderate and Severe Idiopathic Pulmonary Fibrosis: The EME-TIPAC Randomized Clinical Trial. JAMA. 2020;324(22):2282-91.
36. Molyneaux PL, Maher TM. The role of infection in the pathogenesis of idiopathic pulmonary fibrosis. Eur Respir Rev. 2013;22(129):376-81.
37. Selman M, Pardo A. Revealing the pathogenic and aging-related mechanisms of the enigmatic idiopathic pulmonary fibrosis. an integral model. Am J Respir Crit Care Med. 2014;189(10):1161-72.
38. Parimon T, Yao C, Stripp BR, Noble PW, Chen P. Alveolar Epithelial Type II Cells as Drivers of Lung Fibrosis in Idiopathic Pulmonary Fibrosis. Int J Mol Sci. 2020;21(7).

39. Yao C, Guan X, Carraro G, Parimon T, Liu X, Huang G, et al. Senescence of Alveolar Type 2 Cells Drives Progressive Pulmonary Fibrosis. Am J Respir Crit Care Med. 2021;203(6):707-17.
40. Sisson TH, Mendez M, Choi K, Subbotina N, Courey A, Cunningham A, et al. Targeted injury of type II alveolar epithelial cells induces pulmonary fibrosis. Am J Respir Crit Care Med. 2010;181(3):254-63.
41. Xu Y, Mizuno T, Sridharan A, Du Y, Guo M, Tang J, et al. Single-cell RNA sequencing identifies diverse roles of epithelial cells in idiopathic pulmonary fibrosis. JCI Insight. 2016;1(20):e90558.
42. Liang J, Zhang Y, Xie T, Liu N, Chen H, Geng Y, et al. Hyaluronan and TLR4 promote surfactant-protein-C-positive alveolar progenitor cell renewal and prevent severe pulmonary fibrosis in mice. Nat Med. 2016;22(11):1285-93.
43. Chakraborty A, Mastalerz M, Ansari M, Schiller HB, Staab-Weijnitz CA. Emerging Roles of Airway Epithelial Cells in Idiopathic Pulmonary Fibrosis. Cells. 2022;11(6).
44. Duan FF, Barron G, Meliton A, Mutlu GM, Dulin NO, Schuger L. P311 Promotes Lung Fibrosis via Stimulation of Transforming Growth Factor-beta1, -beta2, and -beta3 Translation. Am J Respir Cell Mol Biol. 2019;60(2):221-31.
45. Tomasek JJ, Gabbiani G, Hinz B, Chaponnier C, Brown RA. Myofibroblasts and mechano-regulation of connective tissue remodelling. Nat Rev Mol Cell Biol. 2002;3(5):349-63.
46. Hinz B, Phan SH, Thannickal VJ, Galli A, Bochaton-Piallat ML, Gabbiani G. The myofibroblast: one function, multiple origins. Am J Pathol. 2007;170(6):1807-16.
47. Desmouliere A, Redard M, Darby I, Gabbiani G. Apoptosis mediates the decrease in cellularity during the transition between granulation tissue and scar. Am J Pathol. 1995;146(1):56-66.
48. Bai L, Bernard K, Tang X, Hu M, Horowitz JC, Thannickal VJ, et al. Glutaminolysis Epigenetically Regulates Antiapoptotic Gene Expression in Idiopathic Pulmonary Fibrosis Fibroblasts. Am J Respir Cell Mol Biol. 2019;60(1):49-57.
49. Scruggs AM, Koh HB, Tripathi P, Leeper NJ, White ES, Huang SK. Loss of CDKN2B Promotes Fibrosis via Increased Fibroblast Differentiation Rather Than Proliferation. Am J Respir Cell Mol Biol. 2018;59(2):200-14.
50. Munguia-Reyes A, Balderas-Martinez YI, Becerril C, Checa M, Ramirez R, Ortiz B, et al. R-Spondin-2 Is Upregulated in Idiopathic Pulmonary Fibrosis and Affects Fibroblast Behavior. Am J Respir Cell Mol Biol. 2018;59(1):65-76.
51. Thannickal VJ, Toews GB, White ES, Lynch JP, 3rd, Martinez FJ. Mechanisms of pulmonary fibrosis. Annu Rev Med. 2004;55:395-417.
52. Misharin AV, Budinger GRS. Targeting the Myofibroblast in Pulmonary Fibrosis. Am J Respir Crit Care Med. 2018;198(7):834-5.
53. Fortier SM, Penke LR, King D, Pham TX, Ligresti G, Peters-Golden M. Myofibroblast dedifferentiation proceeds via distinct transcriptomic and phenotypic transitions. JCI Insight. 2021;6(6).
54. Kato K, Logsdon NJ, Shin YJ, Palumbo S, Knox A, Irish JD, et al. Impaired Myofibroblast Dedifferentiation Contributes to Nonresolving Fibrosis in Aging. Am J Respir Cell Mol Biol. 2020;62(5):633-44.
55. Kreuter M, Lee JS, Tzouvelekis A, Oldham JM, Molyneaux PL, Weycker D, et al. Monocyte Count as a Prognostic Biomarker in Patients with Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med. 2021;204(1):74-81.

56. Mills CD. M1 and M2 Macrophages: Oracles of Health and Disease. Crit Rev Immunol. 2012;32(6):463-88.
57. Schupp JC, Binder H, Jager B, Cillis G, Zissel G, Muller-Quernheim J, et al. Macrophage activation in acute exacerbation of idiopathic pulmonary fibrosis. PLoS One. 2015;10(1):e0116775.
58. Marchal-Somme J, Uzunhan Y, Marchand-Adam S, Valeyre D, Soumelis V, Crestani B, et al. Cutting edge: nonproliferating mature immune cells form a novel type of organized lymphoid structure in idiopathic pulmonary fibrosis. J Immunol. 2006;176(10):5735-9.
59. Nuovo GJ, Hagood JS, Magro CM, Chin N, Kapil R, Davis L, et al. The distribution of immunomodulatory cells in the lungs of patients with idiopathic pulmonary fibrosis. Mod Pathol. 2012;25(3):416-33.
60. Todd NW, Scheraga RG, Galvin JR, Iacono AT, Britt EJ, Luzina IG, et al. Lymphocyte aggregates persist and accumulate in the lungs of patients with idiopathic pulmonary fibrosis. J Inflamm Res. 2013;6:63-70.
61. Fireman E, Vardinon N, Burke M, Spizer S, Levin S, Endler A, et al. Predictive value of response to treatment of T-lymphocyte subpopulations in idiopathic pulmonary fibrosis. Eur Respir J. 1998;11(3):706-11.
62. Adegunsoye A, Hrusch CL, Bonham CA, Jaffery MR, Blaine KM, Sullivan M, et al. Skewed Lung CCR4 to CCR6 CD4(+) T Cell Ratio in Idiopathic Pulmonary Fibrosis Is Associated with Pulmonary Function. Front Immunol. 2016;7:516.
63. Francois A, Gombault A, Villeret B, Alsaleh G, Fanny M, Gasse P, et al. B cell activating factor is central to bleomycin- and IL-17-mediated experimental pulmonary fibrosis. J Autoimmun. 2015;56:1-11.
64. Lamas DJ, Kawut SM, Bagiella E, Philip N, Arcasoy SM, Lederer DJ. Delayed access and survival in idiopathic pulmonary fibrosis: a cohort study. Am J Respir Crit Care Med. 2011;184(7):842-7.
65. Hyldgaard C, Hilberg O, Muller A, Bendstrup E. A cohort study of interstitial lung diseases in central Denmark. Respir Med. 2014;108(5):793-9.
66. Cosgrove GP, Bianchi P, Danese S, Lederer DJ. Barriers to timely diagnosis of interstitial lung disease in the real world: the INTENSITY survey. BMC Pulm Med. 2018;18(1):9.
67. Collard HR, Tino G, Noble PW, Shreve MA, Michaels M, Carlson B, et al. Patient experiences with pulmonary fibrosis. Respir Med. 2007;101(6):1350-4.
68. Schoenheit G, Becattelli I, Cohen AH. Living with idiopathic pulmonary fibrosis: an in-depth qualitative survey of European patients. Chron Respir Dis. 2011;8(4):225-31.
69. Wuyts WA, Dahlqvist C, Slabbynck H, Schlesser M, Gusbin N, Compere C, et al. Baseline clinical characteristics, comorbidities and prescribed medication in a real-world population of patients with idiopathic pulmonary fibrosis: the PROOF registry. BMJ Open Respir Res. 2018;5(1):e000331.
70. Hoyer N, Prior TS, Bendstrup E, Wilcke T, Shaker SB. Risk factors for diagnostic delay in idiopathic pulmonary fibrosis. Respir Res. 2019;20(1):103.
71. Hoyer N, Prior TS, Bendstrup E, Shaker SB. Diagnostic delay in IPF impacts progression-free survival, quality of life and hospitalisation rates. BMJ Open Respir Res. 2022;9(1).
72. Lynch DA, Sverzellati N, Travis WD, Brown KK, Colby TV, Galvin JR, et al. Diagnostic criteria for idiopathic pulmonary fibrosis: a Fleischner Society White Paper. Lancet Respir Med. 2018;6(2):138-53.

73. Han Q, Luo Q, Xie JX, Wu LL, Liao LY, Zhang XX, et al. Diagnostic yield and postoperative mortality associated with surgical lung biopsy for evaluation of interstitial lung diseases: A systematic review and meta-analysis. J Thorac Cardiovasc Surg. 2015;149(5):1394-401 e1.
74. Hetzel J, Maldonado F, Ravaglia C, Wells AU, Colby TV, Tomassetti S, et al. Transbronchial Cryobiopsies for the Diagnosis of Diffuse Parenchymal Lung Diseases: Expert Statement from the Cryobiopsy Working Group on Safety and Utility and a Call for Standardization of the Procedure. Respiration. 2018;95(3):188-200.
75. Rodrigues I, Estevao Gomes R, Coutinho LM, Rego MT, Machado F, Morais A, et al. Diagnostic yield and safety of transbronchial lung cryobiopsy and surgical lung biopsy in interstitial lung diseases: a systematic review and meta-analysis. Eur Respir Rev. 2022;31(166).
76. Pankratz DG, Choi Y, Imtiaz U, Fedorowicz GM, Anderson JD, Colby TV, et al. Usual Interstitial Pneumonia Can Be Detected in Transbronchial Biopsies Using Machine Learning. Ann Am Thorac Soc. 2017;14(11):1646-54.
77. Jacobs SS, Krishnan JA, Lederer DJ, Ghazipura M, Hossain T, Tan AM, et al. Home Oxygen Therapy for Adults with Chronic Lung Disease. An Official American Thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med. 2020;202(10):e121-e41.
78. Dowman LM, McDonald CF, Bozinovski S, Vlahos R, Gillies R, Pouniotis D, et al. Greater endurance capacity and improved dyspnoea with acute oxygen supplementation in idiopathic pulmonary fibrosis patients without resting hypoxaemia. Respirology. 2017;22(5):957-64.
79. Dowman LM, McDonald CF, Hill CJ, Lee AL, Barker K, Boote C, et al. The evidence of benefits of exercise training in interstitial lung disease: a randomised controlled trial. Thorax. 2017;72(7):610-9.
80. Dowman L, Hill CJ, May A, Holland AE. Pulmonary rehabilitation for interstitial lung disease. Cochrane Database Syst Rev. 2021;2(2):CD006322.
81. Holland AE, Hill CJ, Glaspole I, Goh N, McDonald CF. Predictors of benefit following pulmonary rehabilitation for interstitial lung disease. Respir Med. 2012;106(3):429-35.
82. Lee JYT, Tikellis G, Corte TJ, Goh NS, Keir GJ, Spencer L, et al. The supportive care needs of people living with pulmonary fibrosis and their caregivers: a systematic review. Eur Respir Rev. 2020;29(156).
83. Kalluri M, Orenstein S, Archibald N, Pooler C. Advance Care Planning Needs in Idiopathic Pulmonary Fibrosis: A Qualitative Study. Am J Hosp Palliat Care. 2022;39(6):641-51.
84. Moor CC, Tak van Jaarsveld NC, Owusuaa C, Miedema JR, Baart S, van der Rijt CCD, et al. The Value of the Surprise Question to Predict One-Year Mortality in Idiopathic Pulmonary Fibrosis: A Prospective Cohort Study. Respiration. 2021;100(8):780-5.
85. Chambers DC, Cherikh WS, Harhay MO, Hayes D, Jr., Hsich E, Khush KK, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-sixth adult lung and heart-lung transplantation Report-2019; Focus theme: Donor and recipient size match. J Heart Lung Transplant. 2019;38(10):1042-55.
86. Kapnadak SG, Raghu G. Lung transplantation for interstitial lung disease. Eur Respir Rev. 2021;30(161).
87. Leard LE, Holm AM, Valapour M, Glanville AR, Attawar S, Aversa M, et al. Consensus document for the selection of lung transplant candidates: An update from the International Society for Heart and Lung Transplantation. J Heart Lung Transplant. 2021;40(11):1349-79.

88. King TE, Jr., Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med. 2014;370(22):2083-92.
89. Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014;370(22):2071-82.
90. Ley B, Swigris J, Day BM, Stauffer JL, Raimundo K, Chou W, et al. Pirfenidone Reduces Respiratory-related Hospitalizations in Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med. 2017;196(6):756-61.
91. Costabel U, Inoue Y, Richeldi L, Collard HR, Tschoepe I, Stowasser S, et al. Efficacy of Nintedanib in Idiopathic Pulmonary Fibrosis across Prespecified Subgroups in INPULSIS. Am J Respir Crit Care Med. 2016;193(2):178-85.
92. Nathan SD, Albera C, Bradford WZ, Costabel U, Glaspole I, Glassberg MK, et al. Effect of pirfenidone on mortality: pooled analyses and meta-analyses of clinical trials in idiopathic pulmonary fibrosis. Lancet Respir Med. 2017;5(1):33-41.
93. Richeldi L, Cottin V, du Bois RM, Selman M, Kimura T, Bailes Z, et al. Nintedanib in patients with idiopathic pulmonary fibrosis: Combined evidence from the TOMORROW and INPULSIS((R)) trials. Respir Med. 2016;113:74-9.
94. Hostettler KE, Zhong J, Papakonstantinou E, Karakiulakis G, Tamm M, Seidel P, et al. Anti-fibrotic effects of nintedanib in lung fibroblasts derived from patients with idiopathic pulmonary fibrosis. Respir Res. 2014;15(1):157.
95. Sato S, Shinohara S, Hayashi S, Morizumi S, Abe S, Okazaki H, et al. Anti-fibrotic efficacy of nintedanib in pulmonary fibrosis via the inhibition of fibrocyte activity. Respir Res. 2017;18(1):172.
96. Wollin L, Maillet I, Quesniaux V, Holweg A, Ryffel B. Antifibrotic and anti-inflammatory activity of the tyrosine kinase inhibitor nintedanib in experimental models of lung fibrosis. J Pharmacol Exp Ther. 2014;349(2):209-20.
97. Kolb M, Bonella F, Wollin L. Therapeutic targets in idiopathic pulmonary fibrosis. Respir Med. 2017;131:49-57.
98. Canestaro WJ, Forrester SH, Raghu G, Ho L, Devine BE. Drug Treatment of Idiopathic Pulmonary Fibrosis: Systematic Review and Network Meta-Analysis. Chest. 2016;149(3):756-66.
99. Rochwerg B, Neupane B, Zhang Y, Garcia CC, Raghu G, Richeldi L, et al. Treatment of idiopathic pulmonary fibrosis: a network meta-analysis. BMC Med. 2016;14:18.
100. Raghu G, Selman M. Nintedanib and pirfenidone. New antifibrotic treatments indicated for idiopathic pulmonary fibrosis offer hopes and raises questions. Am J Respir Crit Care Med. 2015;191(3):252-4.
101. Raghu G, Scholand MB, de Andrade J, Lancaster L, Mageto Y, Goldin J, et al. FG-3019 anti-connective tissue growth factor monoclonal antibody: results of an open-label clinical trial in idiopathic pulmonary fibrosis. Eur Respir J. 2016;47(5):1481-91.
102. Kuttruff CA, Ferrara M, Bretschneider T, Hoerer S, Handschuh S, Nosse B, et al. Discovery of BI-2545: A Novel Autotaxin Inhibitor That Significantly Reduces LPA Levels in Vivo. ACS Med Chem Lett. 2017;8(12):1252-7.
103. Nikolaou A, Kokotou MG, Limnios D, Psarra A, Kokotos G. Autotaxin inhibitors: a patent review (2012-2016). Expert Opin Ther Pat. 2017;27(7):815-29.
104. Palmer SM, Snyder L, Todd JL, Soule B, Christian R, Anstrom K, et al. Randomized, Double-Blind, Placebo-Controlled, Phase 2 Trial of BMS-986020, a Lysophosphatidic Acid

Receptor Antagonist for the Treatment of Idiopathic Pulmonary Fibrosis. Chest. 2018;154(5):1061-9.
105. Maden CH, Fairman D, Chalker M, Costa MJ, Fahy WA, Garman N, et al. Safety, tolerability and pharmacokinetics of GSK3008348, a novel integrin alphavbeta6 inhibitor, in healthy participants. Eur J Clin Pharmacol. 2018;74(6):701-9.
106. Nathan SD, Tapson VF, Elwing J, Rischard F, Mehta J, Shapiro S, et al. Efficacy of Inhaled Treprostinil on Multiple Disease Progression Events in Patients with Pulmonary Hypertension due to Parenchymal Lung Disease in the INCREASE Trial. Am J Respir Crit Care Med. 2022;205(2):198-207.
107. Nathan SD, Behr J, Cottin V, Lancaster L, Smith P, Deng CQ, et al. Study design and rationale for the TETON phase 3, randomised, controlled clinical trials of inhaled treprostinil in the treatment of idiopathic pulmonary fibrosis. BMJ Open Respir Res. 2022;9(1).
108. Polke M, Kondoh Y, Wijsenbeek M, Cottin V, Walsh SLF, Collard HR, et al. Management of Acute Exacerbation of Idiopathic Pulmonary Fibrosis in Specialised and Non-specialised ILD Centres Around the World. Front Med (Lausanne). 2021;8:699644.
109. Naccache JM, Jouneau S, Didier M, Borie R, Cachanado M, Bourdin A, et al. Cyclophosphamide added to glucocorticoids in acute exacerbation of idiopathic pulmonary fibrosis (EXAFIP): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Respir Med. 2022;10(1):26-34.
110. Phillips JE. Inhaled Phosphodiesterase 4 (PDE4) Inhibitors for Inflammatory Respiratory Diseases. Front Pharmacol. 2020;11:259.
111. Matsuhira T, Nishiyama O, Tabata Y, Kaji C, Kubota-Ishida N, Chiba Y, et al. A novel phosphodiesterase 4 inhibitor, AA6216, reduces macrophage activity and fibrosis in the lung. Eur J Pharmacol. 2020;885:173508.
112. Nakagawa N, Barron L, Gomez IG, Johnson BG, Roach AM, Kameoka S, et al. Pentraxin-2 suppresses c-Jun/AP-1 signaling to inhibit progressive fibrotic disease. JCI Insight. 2016;1(20):e87446.
113. van den Blink B, Dillingh MR, Ginns LC, Morrison LD, Moerland M, Wijsenbeek M, et al. Recombinant human pentraxin-2 therapy in patients with idiopathic pulmonary fibrosis: safety, pharmacokinetics and exploratory efficacy. Eur Respir J. 2016;47(3):889-97.
114. Hirani N, MacKinnon AC, Nicol L, Ford P, Schambye H, Pedersen A, et al. Target inhibition of galectin-3 by inhaled TD139 in patients with idiopathic pulmonary fibrosis. Eur Respir J. 2021;57(5).
115. Gagnon L, Leduc M, Thibodeau JF, Zhang MZ, Grouix B, Sarra-Bournet F, et al. A Newly Discovered Antifibrotic Pathway Regulated by Two Fatty Acid Receptors: GPR40 and GPR84. Am J Pathol. 2018;188(5):1132-48.
116. van der Velden JL, Ye Y, Nolin JD, Hoffman SM, Chapman DG, Lahue KG, et al. JNK inhibition reduces lung remodeling and pulmonary fibrotic systemic markers. Clin Transl Med. 2016;5(1):36.
117. Knipe RS, Tager AM, Liao JK. The Rho kinases: critical mediators of multiple profibrotic processes and rational targets for new therapies for pulmonary fibrosis. Pharmacol Rev. 2015;67(1):103-17.
118. Bowman WS, Newton CA, Linderholm AL, Neely ML, Pugashetti JV, Kaul B, et al. Proteomic biomarkers of progressive fibrosing interstitial lung disease: a multicentre cohort analysis. Lancet Respir Med. 2022;10(6):593-602.

119. Aronson KI, Danoff SK, Russell AM, Ryerson CJ, Suzuki A, Wijsenbeek MS, et al. Patient-centered Outcomes Research in Interstitial Lung Disease: An Official American Thoracic Society Research Statement. Am J Respir Crit Care Med. 2021;204(2):e3-e23.
120. Flaherty KR, Wells AU, Cottin V, Devaraj A, Walsh SLF, Inoue Y, et al. Nintedanib in Progressive Fibrosing Interstitial Lung Diseases. N Engl J Med. 2019;381(18):1718-27.
121. Selman M, Pardo A, Wells AU. Usual interstitial pneumonia as a stand-alone diagnostic entity: the case for a paradigm shift? Lancet Respir Med. 2023.