The role of vascularity and the fibrovascular interface in interstitial lung diseases

Jana Dietrich[1,13], Alice Kang[2,13], Birger Tielemans[1], Stijn E. Verleden[3,4], Hassan Khalil[5,6], Florian Länger[1], Philipp Bruners[7], Steven J. Mentzer[5,6], Tobias Welte[8], Michael Dreher[2], Danny D. Jonigk[1,9,10,14] and Maximilian Ackermann[1,11,12,14]

[1]Institute of Pathology, University Clinics Aachen, RWTH University of Aachen, Aachen, Germany. [2]Department of Pneumology and Intensive Care Medicine, University Hospital RWTH Aachen, Aachen, Germany. [3]Antwerp Surgical Training, Anatomy and Research Centre (ASTARC), University of Antwerp, Edegem, Belgium. [4]Department of Respiratory Medicine, University Hospital Antwerp, Edegem, Belgium. [5]Laboratory of Adaptive and Regenerative Biology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA. [6]Department of Thoracic Surgery, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA. [7]Department of Diagnostic and Interventional Radiology, University Hospital RWTH Aachen, Aachen, Germany. [8]Department of Respiratory Medicine and Infectious Disease, Hannover Medical School, Hannover, Germany. [9]Biomedical Research in Endstage and Obstructive Lung Disease Hannover, German Center for Lung Research, Hannover, Germany. [10]Institute of Pathology, Hannover Medical School, Hannover, Germany. [11]Institute of Pathology and Molecular Pathology, Helios University Clinic Wuppertal, University of Witten/Herdecke, Wuppertal, Germany. [12]Institute of Anatomy, University Medical Center of Johannes Gutenberg University Mainz, Mainz, Germany. [13]J. Dietrich and A. Kang share first authorship. [14]D.D. Jonigk and M. Ackermann share senior authorship.

Corresponding author: Maximilian Ackermann (maximilian.ackermann@uni-mainz.de)

Check for updates

Shareable abstract (@ERSpublications)
A review presenting our current understanding of the role of vascularity in the pathogenesis of interstitial lung diseases, emphasising its potential contribution to the exacerbation of fibrosis and its therapeutic implications. https://bit.ly/3NLn4Rg

Cite this article as: Dietrich J, Kang A, Tielemans B, *et al*. The role of vascularity and the fibrovascular interface in interstitial lung diseases. *Eur Respir Rev* 2025; 34: 240080 [DOI: 10.1183/16000617.0080-2024].

Copyright ©The authors 2025

This version is distributed under the terms of the Creative Commons Attribution Non-Commercial Licence 4.0. For commercial reproduction rights and permissions contact permissions@ersnet.org

Received: 12 April 2024
Accepted: 24 Oct 2024

Abstract

Interstitial lung disease (ILD) is a clinical term that refers to a diverse group of non-neoplastic lung diseases. This group includes idiopathic and secondary pulmonary entities that are often associated with progressive pulmonary fibrosis. Currently, therapeutic approaches based on specific structural targeting of pulmonary fibrosis are limited to nintedanib and pirfenidone, which can only slow down disease progression leading to a lower mortality rate. Lung transplantation is currently the only available curative treatment, but it is associated with high perioperative mortality. The pulmonary vasculature plays a central role in physiological lung function, and vascular remodelling is considered a hallmark of the initiation and progression of pulmonary fibrosis. Different patterns of pulmonary fibrosis commonly exhibit detectable pathological features such as morphomolecular changes, including intussusceptive and sprouting angiogenesis, vascular morphometry, broncho-systemic anastomoses, and aberrant angiogenesis-related gene expression patterns. Dynamic cellular interactions within the fibrovascular interface, such as endothelial activation and endothelial–mesenchymal transition, are also observed. This review aims to summarise the current clinical, radiological and pathological diagnostic algorithm for different ILDs, including usual interstitial pneumonia/idiopathic pulmonary fibrosis, non-specific interstitial pneumonia, alveolar fibroelastosis/pleuroparenchymal fibroelastosis, hypersensitivity pneumonitis, systemic sclerosis-related ILD and coronavirus disease 2019 injury. It emphasises an interdisciplinary clinicopathological perspective. Additionally, the review covers current therapeutic strategies and knowledge about associated vascular abnormalities.

Introduction

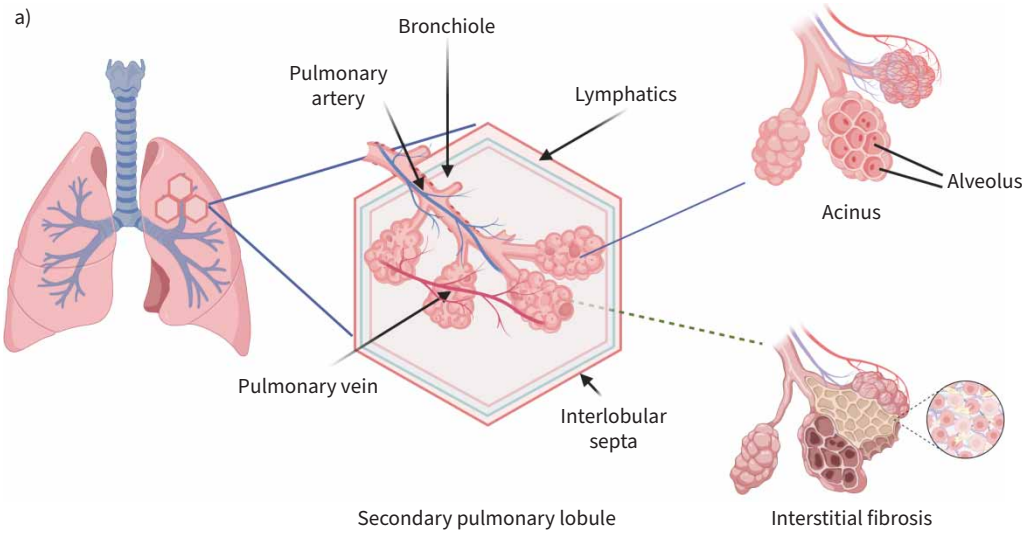
Interstitial lung disease (ILD), or synonymously called diffuse parenchymal lung disease (DPLD), is a diverse group of non-neoplastic lung disease entities that have known or idiopathic aetiology. These diseases primarily affect the pulmonary interstitium through inflammatory and fibrotic lesions, rather than the airspaces, peripheral airways and blood vessels [1–3]. DPLDs of known cause include granulomatous diseases (such as hypersensitivity pneumonitis (HP)), those secondary to connective tissue diseases

(CTDs) (such as systemic sclerosis-related ILD (SSc-ILD) or rheumatoid arthritis-associated ILD (RA-ILD)), exposure-related ILDs (*e.g.* asbestosis, silicosis and post-infectious causes), congenital diseases and other DPLDs such as lymphangioleiomyomatosis or Langerhans cell histiocytosis [1, 4]. The idiopathic interstitial pneumonias (IIPs) represent a group of DPLDs with no apparent cause, whose diagnosis of exclusion is based on clinical, radiological and pathological features [5]. Idiopathic pulmonary fibrosis (IPF) is thereby the most prevalent ILD, accounting for more than a third of cases and accompanied by a high lethality with a median survival of 2–4 years after diagnosis [6, 7].

The diagnostic algorithm of ILDs is based on an interdisciplinary decision-making process involving mainly clinicians, radiologists and pathologists, who form the core team of ILD boards. Anamnesis plays a pivotal role in the diagnostic pathway of ILD. The medical history can reveal a relation to environmental exposure at work or at home, association with reaction to drugs, *etc.* Symptoms may vary among the different kinds of DPLDs. Cough, exertional dyspnoea, fever, weight loss, fatigue and night sweats can appear as the first symptoms. Extrapulmonary manifestations include gastro-oesophageal reflux, dysphagia, arthritis, muscle weakness or skin alterations. In the clinical examination, hourglass nails, nail clubbing, cyanosis and crackle rattle can be observed. More specific clinical manifestations are associated with SSc where fibrosis of the skin and internal organs progresses over the course of the disease. An essential part of the serological diagnostics besides routine clinical chemistry is rheumatological screening, blood eosinophils and precipitins. For radiological diagnostics, chest imaging using high-resolution computed tomography (HRCT) has become an integral part of the differentiation of ILD, taking place early in the diagnostic algorithm. In the case of usual interstitial pneumonia (UIP)/IPF, for example, the presence of typical clinical and HRCT features can lead to the correct diagnosis in >50% without the need for a lung biopsy [1]. If there are unusual radiological characteristics, such as peribronchovascular predominance or predominant ground-glass opacities (GGOs), or atypical clinical findings, such as young age or lack of dyspnoea, a lung biopsy is recommended [5, 8]. Histological patterns provide a better separation of different fibrotic entities than imaging patterns, and based on the early work of Liebow and Carrington (as described in Travis *et al.* [9]), they were the foundation of the first IIP classification. Nevertheless, due to a heterogenous, often peripheral accentuated distribution of fibrotic remodelling within the lung parenchyma the histopathological diagnosis is complicated, especially in transbronchial biopsy specimens, which enable the examination of only small tissue specimens overlaid by artefacts. The American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines advise surgical lung biopsy as the current diagnostic gold standard for ILD, but there is a decent risk of complications such as pneumothorax, bleeding and even mortality which needs to be considered [10]. Transbronchial lung cryobiopsies can be used as an alternative diagnostic tool. In a prospective multicentre study by Troy *et al.* [11], a histopathological agreement of 70.6% was found in comparison to surgical lung biopsies. However, this procedure should be done in expert centres with enough experience in performing cryobiopsies and management of complications such as endobronchial bleeding.

Mechanisms

The smallest independent units of the lungs are the secondary pulmonary lobules, which present the anatomical reference structures for radiological diagnostics (figure 1a). The superordinate bronchiolus terminalis of the bronchovascular bundle conducts air to the related alveoli, where gas exchange takes place. The structure of the alveolocapillary membrane, formed by alveolar epithelial cells (AECs) and capillary endothelial cells (ECs) of the pulmonary microvasculature, both of them sharing a basement membrane, and a small interstitial space, is therefore crucial for sufficient pulmonary function. AECs can be further subdivided into thin pneumocyte type I cells, which are involved in gas exchange, and cuboidal pneumocyte type II cells, alveolar progenitor cells that produce pulmonary surfactant [12, 13]. In terms of pulmonary fibrosis, an abnormal tissue repair process leads to excessive production of extracellular matrix (ECM) within the interstitium [14]. This fibrotic remodelling is initiated by microinjuries of the AECs, *e.g.* due to infection, mechanical damage, autoimmune and allergic reactions or idiopathic origin [15, 16]. The damaged AECs respond with the secretion of profibrogenic factors and cytokines, which finally leads to the recruitment of myofibroblasts as the most important effector cell type of fibrogenesis [17]. Mainly derived from resident fibroblasts, bone marrow-derived fibrocytes or from AECs *via* epithelial–mesenchymal transition (EMT), myofibroblasts represent a reactive cell type that appears in response to acute or chronic injury, typically found in areas of active fibrosis [18, 19]. As their name suggests, myofibroblasts are contractile cells due to their α-smooth muscle actin (SMA)-containing cytoskeleton, which also have a synthetic function that enables the deposition of ECM components, *e.g.* collagen [19–21]. One of the key molecules orchestrating these cellular changes is the profibrotic cytokine transforming growth factor (TGF)-β1, whose importance for pulmonary fibrogenesis has been demonstrated by *in vivo* analysis in rat models and, furthermore, in *in situ* hybridisation and immunohistochemistry of human samples [22, 23]. Based on elevated levels in murine bronchioalveolar lavage (BAL), tissue samples of rat models and human IPF samples, other growth factors involved in the pathophysiology of pulmonary



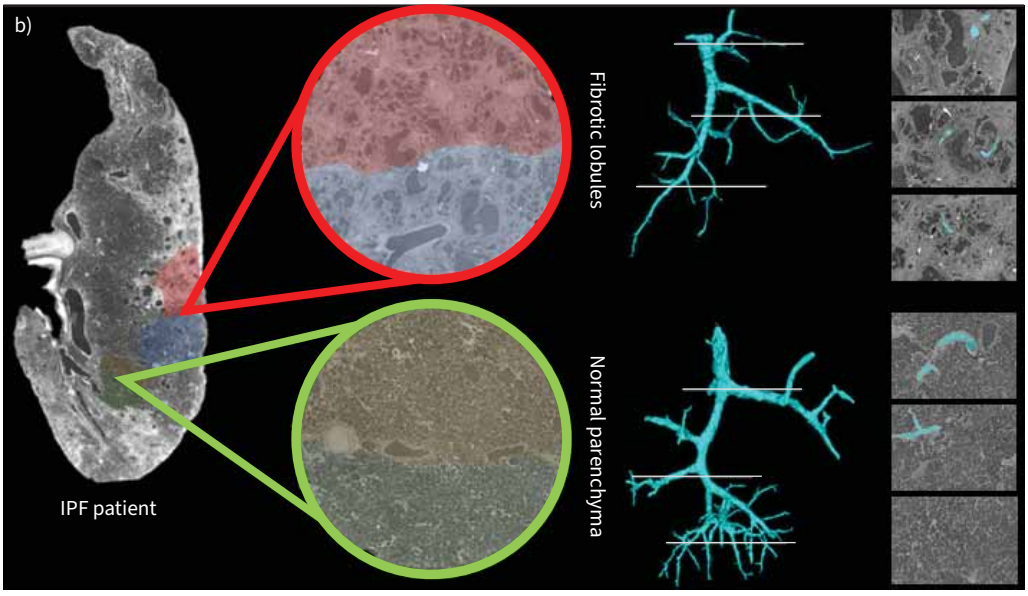


FIGURE 1 a) Schematics of secondary pulmonary lobule anatomy. b) Hierarchical phase-contrast computed tomography (CT) of an explanted idiopathic pulmonary fibrosis (IPF) lung scanned at a resolution of 21.64 µm with two selected volumes of interest (VOI) representing a fibrotic region (red) and a non-fibrotic region (green) imaged at a resolution of 5.06 µm. In the three-dimensional (3D) high-resolution VOI, the fine mesh of pulmonary blood vessels, pulmonary alveoli and their septa can be observed. In each of the VOI, one arterial tree is segmented (green and red circles) down to the pre-capillary level and shown in 3D for both regions. Representative CT slices were made throughout the segmentation. a) Partially created with BioRender.com.

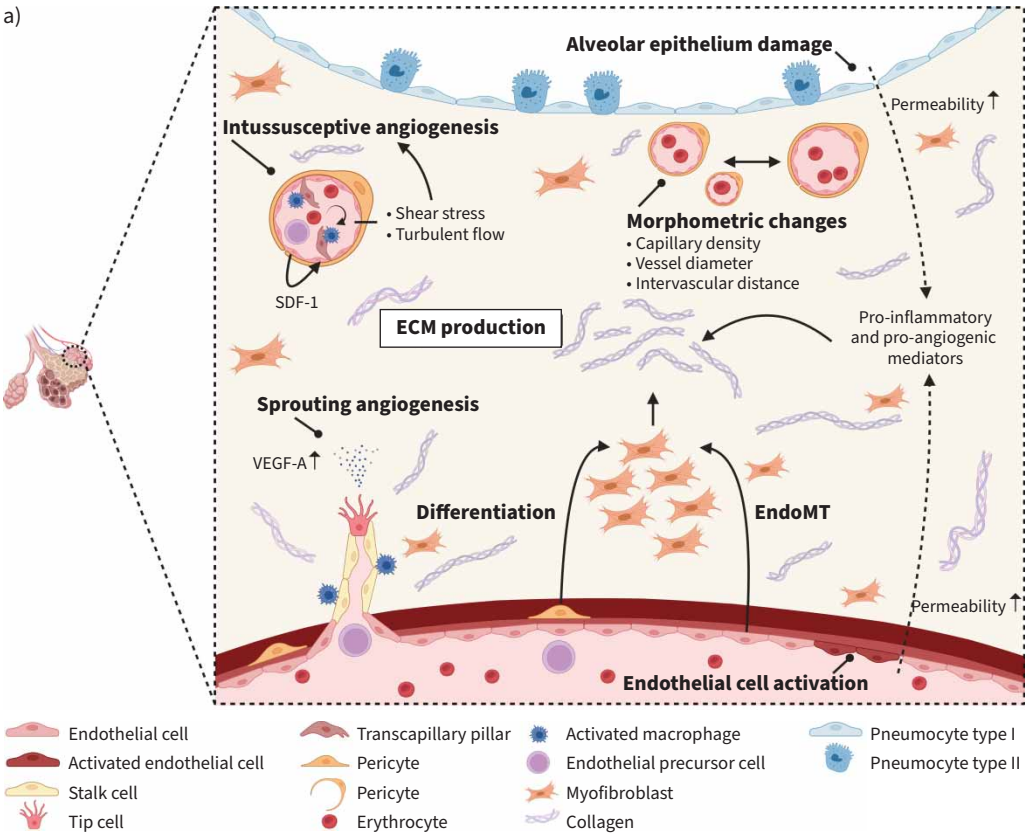
fibrosis are vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF) [24–26]. *Ex vivo* models using human precision-cut lung slices, which were treated with TGF-β, tumour necrosis factor (TNF)-α, PDGF-AB and lysophosphatidic acid (LPA) to induce fibrotic remodelling, demonstrated upregulation of the tissue remodelling factors connective tissue growth factor (CTGF) and matrix metalloprotease (MMP) 7 [27]. Other subtypes of ECM remodelling enzymes, MMP2, MMP7, MMP12, MMP14, MMP19 and lysyl oxidase-like, have been linked to fibrosis in different histological patterns of human fibrotic lung samples and in murine bleomycin-induced pulmonary fibrosis [28, 29]. Moreover, *ex vivo* studies on precision-cut lung slices have demonstrated an upregulation of the pro-inflammatory mediators interleukin (IL)-1β and WNT5a during fibrotic remodelling [27]. In addition, *in vitro* studies analysing the supernatant of cultivated IPF fibroblasts demonstrated elevated levels of the pro-inflammatory cytokines TNF-α, interferon-γ and IL-8 [30]. In human and murine fibrotic tissue, an upregulation of chemokines, *e.g.* CXCL1 and CXCL12, and adhesion molecules, *e.g.* E-selectin,

has been demonstrated [29, 31]. This enables the infiltration of immune cells of the innate and adaptive immune system to the site of injury. Macrophages represent the predominant cell type of inflammatory infiltrates in histopathological UIP and non-specific interstitial pneumonia (NSIP) patterns of human tissue samples, especially within fibrotic lesions [29]. In general, macrophages are resident cells of the innate immune system, located in both the alveoli and the interstitium of the fibrovascular interface [18]. Based on single-cell RNA sequencing (scRNAseq) data of eight lung explants from patients with pulmonary fibrosis of different aetiology, a 2019 study by Reyfman *et al.* [32] identified a subpopulation of alveolar macrophages exclusively found in pulmonary fibrosis characterised by differential gene expression, *e.g. IL1RN*. Macrophages respond to innate immune ligands present in pathogen- or danger-associated molecular patterns to adopt fibrosis-modifying properties. On the other hand, macrophages may inhibit fibrosis by stimulating a regenerative programme in epithelial stem cells, modulating MMPs and tissue inhibitors of MMPs (TIMPs), and directly degrading collagen and ECM [33]. Besides macrophages, a variable infiltration of T- and B-lymphocytes, whose distribution can vary spatially both within one lesion and also between different entities, has been shown in human fibrotic lungs [29]. Different lymphocytic subtypes vary regarding their contributive effect on fibrogenesis and the findings are partially contradictory [34, 35]. In addition to the previously described cell types typically found in fibrosis-associated inflammatory infiltrates, there is evidence that neutrophils may also be involved in fibrogenesis. Elevated levels of neutrophil elastase (NE) were detected in BAL samples of IPF patients [36]. With regard to their potential role in lung fibrogenesis, studies have demonstrated the effect of NE on fibroblast proliferation *in vitro* and furthermore on the promotion of myofibroblast differentiation in mouse models [36, 37]. Similar effects have been shown *in vitro* for neutrophil extracellular trap release on human lung fibroblasts [38]. In addition, blood levels of neutrophils may serve as a prognostic marker in ILDs. A multicentre, retrospective observational study of patients with IIP has demonstrated the utilisation of the lung immune prognostic index, which is calculated from the blood lactate dehydrogenase level and derived neutrophil/lymphocyte ratio, as a predictive tool for survival in patients with IPF [39]. An elevated neutrophil/lymphocyte ratio in peripheral blood samples was associated with higher mortality risk in a cohort of patients suffering from idiopathic pleuroparenchymal fibroelastosis (iPPFE) [40]. In conclusion, immune cell subtypes of the fibrovascular interface seem to be relevant mediators for fibrogenesis.

Growing evidence indicates a pivotal role of the vascular compartment for progression of fibrotic changes based on cellular and molecular-driven interactions within the fibrovascular interface. Fibrosis-associated changes in the pulmonary vasculature (figure 1b) could therefore not just act as a bystander alteration, but beyond that as a driver mechanism in pulmonary fibrosis.

Microvasculature of the fibrovascular interface

The lungs are characterised by a dual blood supply: the systemic circulation supplies the pleura and large airways with oxygen, while the pulmonary circulation forms the vascular part of the alveolocapillary membrane and is therefore responsible for gas exchange [41, 42]. According to scRNAseq data, the pulmonary ECs can thereby be separated into two distinct populations: aerocytes, mainly involved in gas exchange, and general capillary ECs, functioning as stem/progenitor cells [42, 43]. Structural aberrations of the vasculature in human specimens of pulmonary fibrosis were first described by Turner-Warwick [44] in 1963, who reported the formation of pre-capillary anastomoses between pulmonary and systemic arteries, mainly in subpleural regions based on microradiographic studies. The presence of additional functional aberrations was shown by Takabatake *et al.* [45], who demonstrated different ^{123}I-metaiodobenzylguanidine scintigraphy uptake rates in a cohort of 23 patients with IPF and CTD-pulmonary fibrosis indicative for EC injury with increased vascular permeability. It is probable that alveolar injury will directly affect ECs in pulmonary fibrosis. In murine models of bleomycin-induced lung injury, ECs have been observed to upregulate paracrine profibrotic molecules, including plasminogen activator inhibitor-1, TGF-β, PDGF and CTGF [31, 46]. Additionally, these cells have been shown to lose their ability to generate both nitric oxide synthase and prostacyclin. Moreover, the overexpression of adhesion molecules (*e.g.* E-selectin and P-selectin) and chemokines (*e.g.* CXCL1, CXCL2, CCL2 and CCL3) enabling the homing and extravasation of immune cells to sites of injury has been shown [31]. Based on scRNAseq data in mouse models of lipopolysaccharide-induced acute lung injury, Zhang *et al.* [47] demonstrated the presence of a dynamic EC subpopulation that predominantly expresses immune response genes (immune ECs), *e.g. HLA-A*, which may have a main regulatory function in terms of inflammatory injury. Endothelial expression of stromal cell-derived factor (SDF)-1 (CXCL2) recruits CXCR4$^+$ and Tie-2$^+$ bone marrow-derived mononuclear cells and mediates the adhesion of circulating CD34$^+$ progenitor cells [48]. The release of pro-angiogenic mediators stimulates the haematopoietic vascular niche through angiocrine recruitment of monocytes (CD11b/Tie-2$^+$) and circulating endothelial progenitor cells (EPCs) [49–51], and activation of perivascular macrophages (VEGFR1$^+$) or perivascular fibroblasts (Jag1$^+$) [52]. In addition to EC activation, endothelial–mesenchymal transition (EndoMT) is another mechanism by which the vasculature contributes to pulmonary fibrosis (figure 2a): ECs



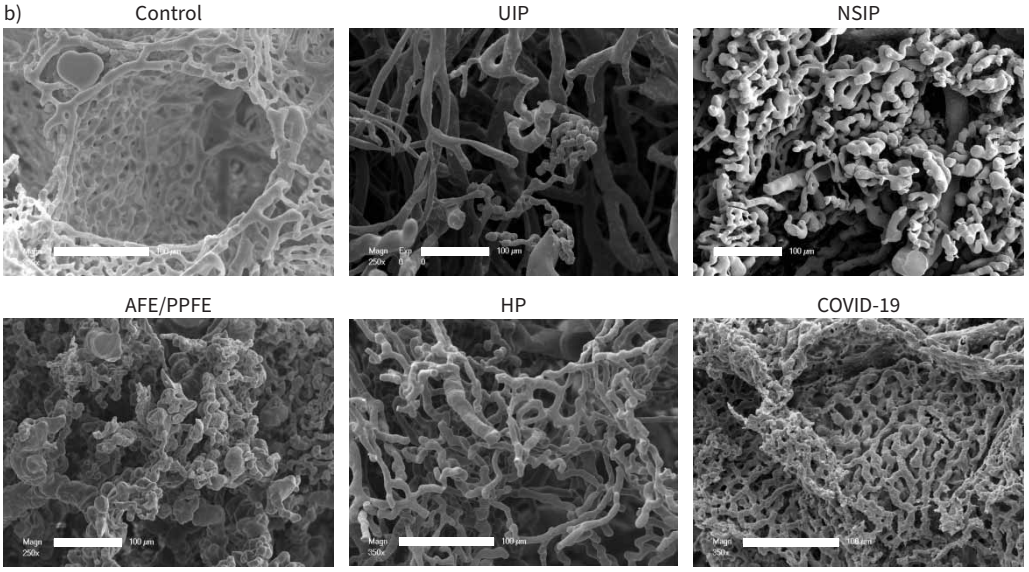


FIGURE 2 a) Schematic illustration of dynamic core interactions and vascular aberrations within the fibrovascular interface of pulmonary fibrosis. SDF: stromal cell-derived factor; ECM: extracellular matrix; VEGF: vascular endothelial growth factor; EndoMT: endothelial–mesenchymal transition. b) Scanning electron micrographs of microvasculature corrosion casts show variable architectural disorders in different patterns of pulmonary fibrosis. The microvasculature of the healthy control lung forms a homogeneous network of thin-walled capillaries surrounding the alveoli. The usual interstitial pneumonia (UIP) lung illustrates aberrant microvasculature based on blind-ending, partially occluded vessels with increased vessel diameters, intervascular distances and vessel sprouts. The non-specific interstitial pneumonia (NSIP) lung shows tufted, tortuous vessels with increased intussusceptive angiogenesis. The microvasculature of the alveolar fibroelastosis/pleuroparenchymal fibroelastosis (AFE/PPFE) lung resembles the NSIP lung. The hypersensitivity pneumonitis (HP) lung presents decreased angiogenesis in more affected, fibrotic areas. The coronavirus disease 2019

(COVID-19) injury lung shows loss of vessel hierarchy based on elongated and deformed capillaries with calibre changes and additionally increased intussusceptive but also sprouting angiogenesis. Scale bars: 100 µm. a) Partially created with BioRender.com. b) Partially reproduced from [91] with permission.

undergo transdifferentiation into myofibroblasts during EndoMT, as indicated by a loss of endothelial markers, *e.g.* CD31, CD34 and VE-cadherin, and a gain of mesenchymal markers, *e.g.* α-SMA and fibronectin [53]. The process of EndoMT is regulated by various factors including TGF-β, Ras, IL-1β, TNF-α, Wnt, Notch and PDGF [53, 54]. In addition to ECs, pericytes are another cell type of the fibrovascular interface that represent a potential source of myofibroblasts: pericytes display periendothelially located smooth muscle cells of the microvasculature [55]. These pericytes are considered a type of mesenchymal stem cell with the ability to differentiate into various cell types, including myofibroblasts [56], which may occur through a TGF-β1-dependent mechanism [57]. In addition to the previously described aberrations and dynamic actions within the cellular compartments of the fibrovascular interface, several types of pulmonary fibrosis exhibit angiogenesis-related vascular remodelling of the pulmonary microvasculature. The term "angiogenesis" refers to the remodelling and formation of new blood vessels from pre-existing vasculature, based on sprouting or intussusceptive (non-sprouting) angiogenesis. Sprouting angiogenesis is an EC response mechanism to angiogenic growth factors, such as VEGF-A, resulting in EC proliferation, degradation of the surrounding ECM and connection with surrounding vessel formation (figure 2a) [49, 58, 59]. The EC projections protrude towards growth factor diffusion gradients, specifically VEGFR2, and maintain two cellular subtypes [60]: non-proliferative tip cells, which are mainly responsible for migration in the surrounding ECM, and proliferative stalk cells [61]. In contrast, intussusceptive angiogenesis is a non-proliferative and highly dynamic mechanism based on EC reorganisation. This mechanism enables the microcirculation to adapt quickly to turbulent blood flow and shear stress (figure 2a) [49–51]. It occurs in capillaries, smaller arteries and veins [59, 62]. Intussusceptive angiogenesis enables vessel duplication, remodelling of branching angles and vessel pruning [63]. This process is initiated by contact between ECs of opposite vessel walls, leading to the formation of intravascular tissue pillars that span the vessel lumen perpendicularly to the direction of blood flow [63–65]. The formation of pillars can be detected by corrosion casting and scanning electron microscopy (SEM) as a hole in the luminal cast (figure 2b) [62, 66].

Role of endothelial precursors in pulmonary angiogenesis

In recent years, there has been an increased interest in EPCs due to their potential therapeutic benefits in cardiovascular medicine and as biomarkers of vascular senescence [67–70]. The groundbreaking work of Asahara *et al.* [71] in 1997 described the isolation of $CD34^+/VEGFR2^+$ ECs from human peripheral blood that formed sprouting angiogenic cell clusters, leading to the discovery of EPCs. This discovery raises questions about their origin. Yoder *et al.* [72] identified endothelial progenitor colony-forming cells (ECFCs), which are a type of vascular resident EC with high pro-angiogenic potency. ECFCs are derived from a non-haematopoietic origin and are characterised by high proliferative activity, forming tube-like structures or sprouts. On the other hand, myeloid angiogenic cells are non-proliferative and non-sprouting cells that enable angiogenesis through intussusception or paracrine effects [73]. Several factors, such as SDF-1 [74], thrombin receptor PAR1 [75], VEGF-A [76], TGF-β1 [77], nestin [78] and osteoprotegerin [79], are known to stimulate ECFCs. Therapeutic use of ECFCs can improve vascularisation in chronic lung diseases [80, 81]. Additionally, ECFCs can be used to monitor the course and progression of lung diseases such as COPD [82] and pulmonary fibrosis [83, 84]. Smadja [70] conducted a study on the impact of ECFCs as a liquid biomarker in patients with IPF, showing that ECFCs isolated from IPF patients exhibited accelerated senescence and increased apoptosis. Additionally, ECFCs were found to be significantly higher in patients with impaired diffusing capacity of the lung for carbon monoxide (D_{LCO}). Soluble factors released from ECFCs isolated from IPF patients provide evidence of stimulating fibroblast migration and activation through higher levels of plasminogen and CXCL8 [84, 85]. Increased ECFC proliferation was observed in exacerbation of IPF or reduced lung function in SSc-ILD, in contrast to stable disease [86]. Clinical studies have shown that there is cross-talk between the proliferation of ECFCs and fibrocytes, which are haematopoietic-derived cells that produce collagen following lung injury, during disease and thus directly contribute to fibrosis [74]. It is expected that ECFCs will serve as a surrogate marker for pulmonary angiogenesis in chronic lung diseases.

In summary, the preceding considerations clarify the multifactorial and complex interactions between different compartments of the fibrovascular interface, indicating a strong association between pulmonary vasculature and angiogenesis, on the one hand, and pulmonary fibrogenesis, on the other hand. Moving forward, current diagnostic algorithms should be synchronised with aberrations in the fibrovascular interface in specific entities of pulmonary fibrosis.

Usual interstitial pneumonia

The prevailing hypothesis regarding the pathophysiology of IPF posits that recurrent damage to the alveolar epithelium results in fibroblast activation, which is consistent with the characteristic morphological pattern of UIP. The UIP pattern is the hallmark radiological and histological pattern of IPF [87]. HRCT features frequently seen in the UIP pattern include honeycombing and traction bronchiectasis/bronchiolectasis, which may be seen at the same time with mild GGOs and fine reticulation (figure 3a). Radiologically, the classical UIP pattern is associated with a subpleural and basal-predominant reticular abnormality with volume loss. According to the current ATS/ERS classification, the clinico-radiological-pathological diagnosis of IPF is related to the histomorphological pattern of UIP [88]. The definite histopathological diagnosis of "UIP" is thereby made up by the combined presence of the following diagnostic features: a patchy pattern of dense interstitial fibrosis indicating spatial heterogeneity, fibroblastic foci of proliferating myofibroblasts correlating

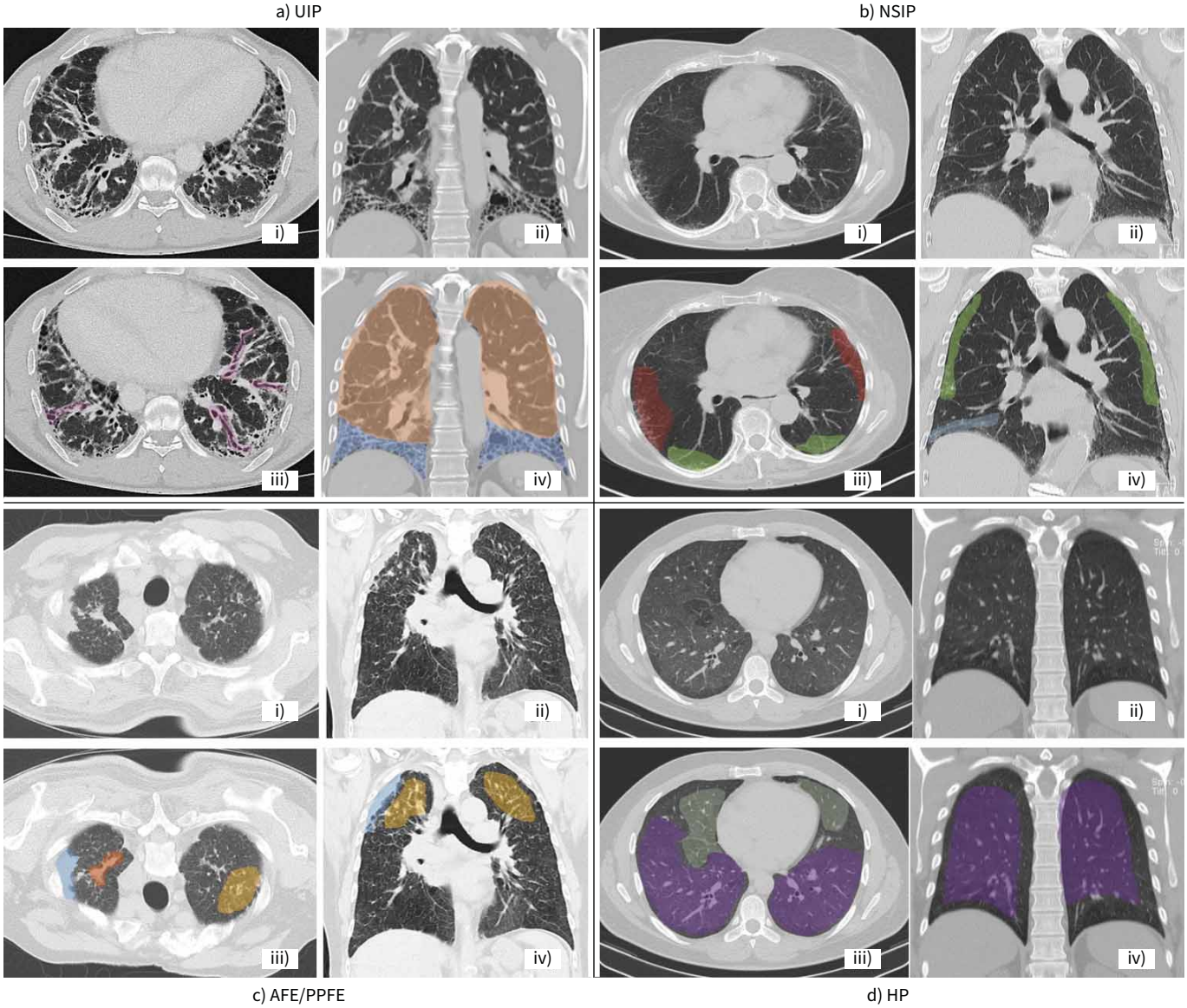


FIGURE 3 a) Usual interstitial pneumonia (UIP) pattern: subpleural changes with an apicobasal gradient (peach), honeycombing (blue), traction bronchiectasis (pink) and focal ground-glass opacities (GGOs). b) Non-specific interstitial pneumonia (NSIP) pattern: symmetrical subpleural changes without an apicobasal gradient (green), peripheral GGOs (red), linear/reticular opacities (blue), "microcystic honeycombing" and micronodules. c) Alveolar fibroelastosis/pleuroparenchymal fibroelastosis (AFE/PPFE) pattern: apical caps (brown), pleural apical bilateral thickening (blue) and apical subpleural fibrosis (yellow). d) Hypersensitivity pneumonitis (HP) pattern: homogeneous GGOs, mostly bilateral and symmetrical (violet), mosaic perfusion (green), air trapping and centrilobular nodules. For each pattern, panels i) and ii) show axial and coronal computed tomography images, with coloured overlays indicating the subpleural changes shown in the corresponding panels iii) and iv).

to temporal heterogeneity and architectural disorders (*i.e.* microscopic honeycombing with the formation of cystic airspaces containing mucus and inflammatory cells) (figure 4). According to the radiological description, the histological UIP pattern shows a predominant distribution in subpleural and paraseptal parenchyma. The diagnosis of IPF is then based on an interdisciplinary agreement with the presence of the HRCT and histological pattern of UIP and exclusion of a known aetiology of ILD [10]. With regard to the vascular contribution to fibrogenesis, Ebina *et al*. [89] demonstrated a heterogeneity of vascular remodelling in human IPF samples using morphometric approaches. Their observations indicate a negative correlation between the degree of fibrosis and the vascular capillary density in lung specimens of patients with IPF, whereas post-capillary venules were increased in central fibrotic areas next to adjacent secondary pulmonary lobules. Fibroblastic foci were characterised by a lack of capillary vessels. This morphological observation related to an increased expression of the angiostatic factor pigment epithelium-derived factor compared to an almost undetectable expression of VEGF, functioning as an angiogenic mediator [90]. SEM of microvasculature corrosion casts indicates similarities to the tumour microvasculature in IPF. These similarities are characterised by blind-ending and partially occluding vessels, reduction of vessel density and, compared to healthy control, NSIP and alveolar fibroelastosis (AFE) samples, significantly increased vessel

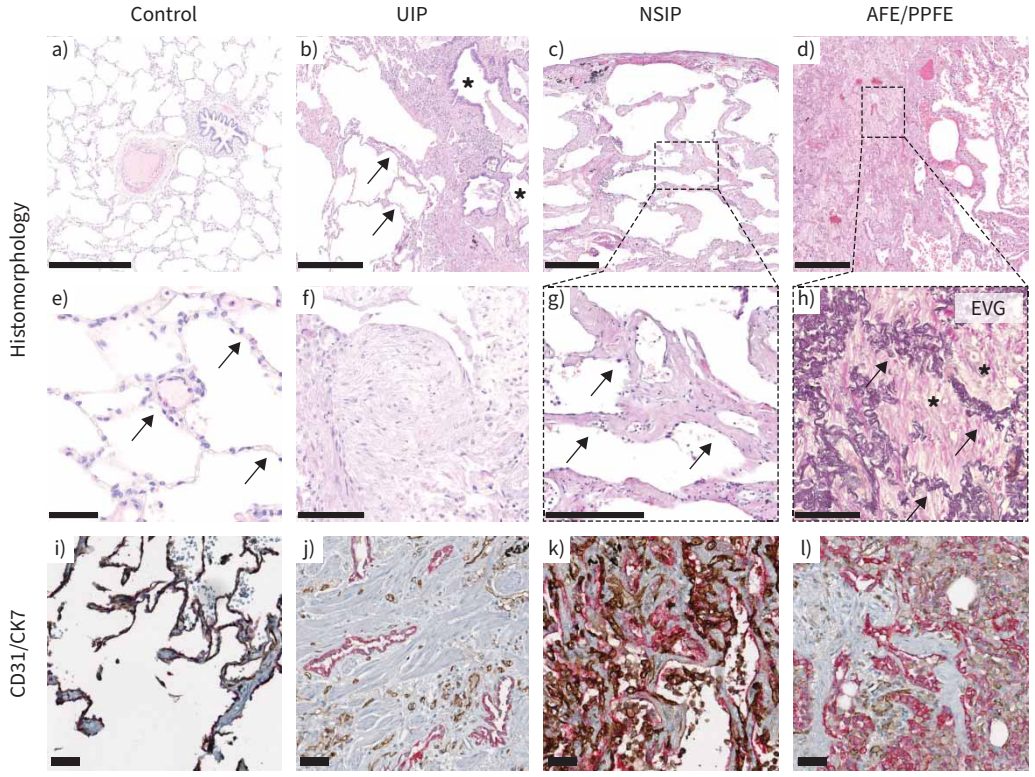


FIGURE 4 a–h) Histomorphology in different patterns of pulmonary fibrosis and i–l) immunohistochemical protein expression of CD31/CK7 in a, e, i) controls, b, f, j) usual interstitial pneumonia (UIP), c, g, k) non-specific interstitial pneumonia (NSIP) and d, h, l) fibroelastosis/pleuroparenchymal fibroelastosis (AFE/PPFE). a) Normal lung parenchyma reveals homogeneous formed airspaces adjacent to bronchovascular bundles. e) Thin alveolar septa (arrows) of normal lung parenchyma containing small capillaries. b) Histological pattern of UIP shows patchy, collagenous interstitial fibrosis with cystic, mucus-containing airspaces (asterisks) beside thin alveolar septa (arrows) indicating spatial heterogeneity. f) Fibroblastic foci in the UIP pattern represent temporal heterogeneity. c) Overview of the histological NSIP pattern shows homogeneous widening of alveolar septa. g) At higher magnification this is due to mild interstitial fibrosis (arrows). d) Overview of AFE/PPFE lung parenchyma presents a homogeneous and continuous, dense fibrosis. h) At higher magnification this is attributable to alveolar obstruction by intra-alveolar collagen deposits (asterisks) and prominent elastosis of the former alveolar septa (arrows). i–l) Associated with a variable morphology of pulmonary fibrosis in UIP, NSIP and AFE/PPFE, double-staining against CK7-expressing bronchoalveolar epithelium (red) and CD31-expressing endothelial cells (brown) indicates a spatial heterogeneity of vascularisation. Scale bars: a–c) 500 µm; d, g) 250 µm; f, h) 100 µm; e, i–l) 50 µm. EVG: Elastic Van Gieson stain. Partially reproduced from [91] with permission.

diameters and intervascular distances (figure 2b). Additionally, IPF is associated with increased sprouting angiogenesis starting from blind-ended vessels towards fibroblast foci [91]. Beyond the morphometric aberrations, IPF lungs show cellular aberrations of the microvasculature. Adams *et al.* [92] identified an increased COL15A1$^+$ EC population histologically related to areas with dense fibrosis or surrounding fibroblastic foci, which is usually restricted to the peribronchial vasculature. Based on a bleomycin-induced pulmonary fibrosis mouse model, Hashimoto *et al.* [53] revealed TGF-β and RAS-associated EndoMT in IPF, which could explain the lack of vasculature in active fibroblastic foci. Immunohistochemically based, descriptive analysis by Gaikwad *et al.* [93] demonstrated increased mesenchymal (N-cadherin, S100A4 and vimentin) and myofibroblast-associated (α-SMA) marker expression in pulmonary arteries accompanied by aberrant expression of endothelial markers (VE-cadherin) in IPF compared to control lungs, possibly indicative for EndoMT. Besides ECs, pericytes may also contribute to fibrogenesis in IPF. Sava *et al.* [57] identified a subpopulation of myofibroblasts in IPF expressing pericyte marker NG2 indicative for pericyte transdifferentiation. Gene expression analyses revealed a significant upregulation of *SGK196* and *MAST2* in IPF, which appear to be involved for pulmonary vascular remodelling [94]. Moreover, the transcription factor *FOXF1*, which usually maintains the EC barrier, shows a decreased expression in fibrotic areas of human IPF and bleomycin-injured murine lungs associated with increased endothelial permeability, a potential driver for fibrogenesis [95].

Non-specific interstitial pneumonia

NSIP describes a radiological and histological pattern as well as a clinical diagnosis belonging to the group of IIPs. Idiopathic NSIP (iNSIP) is a rare diagnosis requiring exclusion of other causes such as an underlying CTD, toxins and numerous other causes. In most patients with NSIP, CT scans demonstrate GGOs with subpleural sparing, reticular opacities, thickening of bronchovascular bundles and traction bronchiectasis, with varied amounts of interstitial changes and honeycombing in fibrotic NSIP (figure 3b) [8]. The histology of NSIP covers a spectrum between a cellular/inflammatory and fibrotic pattern leading to a diffuse, homogeneous widening of the alveolar septa caused by a varying degree of prominent interstitial inflammation with lymphoid aggregates and mild interstitial fibrosis (figure 4) [96–98]. In contrast to UIP, the fibrotic pattern affects the lung homogeneously, which preserves the lung architecture. Temporal heterogeneity of the fibrotic stroma and therefore the presence of fibroblastic foci is uncommon [88]. SEM of microvasculature corrosion casts indicates vascular remodelling in NSIP samples presented by tufted vessels with increased tortuosity (figure 2b). Spatially associated with the widened alveolar septa, the NSIP pattern is accompanied by a higher amount of intussusceptive angiogenesis in comparison with the UIP and AFE patterns [91]. On a molecular level, NSIP reveals an increased gene expression of Thy1/CD90, a receptor expressed on ECs and probably involved in intussusceptive angiogenesis [91, 99, 100]. Besides the morphological changes, recent evidence suggests additional cellular aberrations in the pulmonary microvasculature. In lung specimens of fibrotic NSIP, Schupp *et al.* [101] demonstrated alveolar vascular remodelling based on the replacement of pulmonary non-fenestrated ECs with a fenestrated COL15A1$^+$ EC population, accompanied by larger vessel diameter.

Alveolar fibroelastosis/pleuroparenchymal fibroelastosis

AFE, also called PPFE, displays another radiological and histological fibrotic pattern. AFE has been described in terms of several clinical settings, *e.g.* chronic lung allograft dysfunction as a complication of bone marrow or lung transplantation, chemotherapy, in association with CTD or mostly as an idiopathic disease (iPPFE) [102–105]. In radiological diagnostic algorithms PPFE is defined as either definite, by pleural thickening with associated subpleural fibrosis concentrated in the upper lobes (apical caps) with involvement of lower lobes being less marked or absent, or consistent, indicated by upper lobe pleural thickening with associated signs of subpleural fibrosis present but no upper lobe predominance (figure 3c) [98]. PPFE frequently exists as a co-injury pattern with other pathological patterns, such as UIP [98]. The AFE/PPFE histological fibrotic pattern represents a more recently identified pattern, which was first described in 2004 by Frankel *et al.* [106]. It is characterised by a homogenous alveolar obstruction due to intra-alveolar collagen deposition with a prominent elastosis of the former alveolar walls (figure 4). The fibrotic changes affect predominantly the subpleural regions, especially in clinically benign apical cap lesions, accompanied by a prominent fibrotic thickening of the adjacent visceral pleura [106, 107]. In iPPFE and secondary PPFE, fibroelastosis also involves the interlobular septa and the bronchovascular bundles showing a deeper penetration into the pulmonary parenchyma with a pronounced para-arterial and para-bronchial distribution [108]. A mild and patchy lymphoplasmocytic infiltrate as well as fibroblastic foci can be seen [106–108]. Corrosion casting of the microvasculature in AFE specimens reveals densely packed and partially compressed vessels with increased tortuosity, comparable to those seen in NSIP (figure 2b). Additionally, AFE is associated with an upregulation of the angiogenesis-related Thy1/CD90 gene already mentioned in NSIP [91]. An histomorphometric-based study by Kinoshita *et al.* [109] indicated remodelling of the pulmonary artery in iPPFE: comparing iPPFE with IPF and control samples

they suggest arterial medial elastosis and collagenous thickening of the adventitia as distinct features of macrovascular changes related to iPPFE.

Hypersensitivity pneumonitis

HP is classified as a non-infectious granulomatous disease affecting the lung parenchyma and the small airways. HP is typically caused by an immune-mediated reaction to an inhaled antigen such as mould or bird feathers in susceptible individuals, but an inciting antigen is not found in 30–50% of cases evaluated in ILD referral centres [110–113]. The current ATS/Japanese Respiratory Society/Asociación Latinoamericana del Tórax clinical practice guideline categorises HP as either non-fibrotic/cellular, *e.g.* predominantly inflammatory, or fibrotic [114]. HP is more prevalent among older individuals (aged >65 years), but is still a fairly rare disease. Patients with fibrotic HP tend to have a reduced vital capacity, lower D_{LCO} and lower numbers of lymphocytes in BAL than patients with non-fibrotic HP. Non-fibrotic HP presents with GGOs that may be diffuse or only present as centrilobular nodules, along with evidence of air trapping (figure 3d) [115]. Fibrotic HP, on the other hand, includes features of fibrosis such as a reticular pattern, traction bronchiectasis and honeycombing, as well as bronchiolar obstruction with mosaic attenuation and air trapping, particularly in CT scans acquired during expiratory breath-hold. The histopathological diagnosis of non-fibrotic HP is based on the concordance of a pathognomonic triad: lymphocyte-predominant interstitial pneumonia with bronchiolocentric distribution, poorly formed granulomas and cellular bronchiolitis with optional evidence of organising pneumonia [98, 114]. Histological features of fibrotic HP include subpleural and centriacinar fibrosis, possibly with bridging fibrosis spanning several neighbouring lesions. Heterogenous fibrosis with fibroblast foci and honeycombing as well as fibrotic NSIP-like fibrosis can also be seen [114]. Currently, there is only limited knowledge regarding vascular changes in HP. Initial findings in human samples of fibrotic HP indicate decreased angiogenesis in more affected lung zones compared to increased angiogenesis in less affected areas based on SEM of microvasculature corrosion casts (figure 2b) [116].

Systemic sclerosis-associated interstitial lung disease

SSc is a rare autoimmune CTD with an estimated global prevalence of 3–24 per 100 000. The pathophysiology is characterised by fibroblast dysfunction and deposition of excessive ECM leading to microvascular damage with progressive fibrosis of the skin and internal organs potentially causing skin thickening, telangiectasis, fingertip ulcers, oesophageal dysmotility, and cardiac and pulmonary involvement. Thereby, the pulmonary manifestations have the highest mortality in SSc among CTDs. The most common radiological and histological pattern of lung fibrosis in SSc is NSIP, and less frequently UIP [88, 117–119]. Diffuse fibrosis with subpleural sparing affects mostly the lower lobes. GGOs are observed frequently. Based on immunohistochemical detection of endothelial CD34 expression, Franco de Carvalho *et al*. [120] indicated a significantly decreased microvessel density in SSc-NSIP compared to iNSIP, accompanied by a higher vascular activity measured by vascular cell adhesion molecule-1 expression possibly indicative of differences in vascular remodelling. Mendoza *et al*. [121] identified $CD31^+$ ECs in the neointima of small vessels, perivascular tissue and also in lung parenchyma besides cells characterised by coexpression of ECs and mesenchymal cell markers in small- and medium-sized arterioles in SSc-ILD, which could be indicative of EndoMT involvement in the pathogenesis.

COVID-19 injury pattern

The COVID-19 pandemic in 2019 was due to the infectious severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, which leads to variable common clinical symptoms ranging from fever, dry cough, fatigue to severe cases of acute respiratory distress syndrome (ARDS) based on COVID-19 pneumonia. At the onset of the pandemic, CT imaging of COVID-19 pneumonia typically revealed a predominantly peripheral, middle and lower posterior distribution [122]. However, with the mutation of the SARS-CoV-2 virus over time and increased immunogenicity, radiological changes became less typical. ARDS in general represents a clinical syndrome based on microvascular lung injuries observed in the setting of different risk factors, *e.g.* pneumonia, non-pulmonary sepsis, severe trauma, pancreatitis or non-cardiogenic shock [123]. Based on the time-dependent changes of the correlating histological pattern of diffuse alveolar damage (DAD), it can be subdivided into three phases: the early exudative phase, the organising phase and the fibroproliferative phase, which possibly leads to intra-alveolar and interstitial pulmonary fibrosis [124]. Autopsy studies have shown that fibrosis is thereby more frequent in patients with ARDS due to pulmonary origin (*e.g.* pneumonia or aspiration) [125]. The fibrotic changes are accompanied by vascular aberrations. Already back in 1983, based on autopsy specimens of patients suffering from ARDS, Tomashefski *et al*. [126] specified pulmonary vascular remodelling with tortuous, thick-walled vessels concentrated in areas of dense fibrosis besides reduced but dilated capillaries leading to secondary pulmonary hypertension. The vascular changes correlate with the duration of ARDS and thereby with the incidence of fibrosis more than with the underlying cause. Due to its dynamic urgency,

research in recent years has focused on deciphering the pathophysiology of COVID-19. So, in contrast to other risk factors for ARDS and associated fibrotic changes, there are specific findings about vascular-associated changes in severe COVID-19. In the early phase of severe COVID-19, the histological appearance of lung specimens is characterised by the exudative phase of DAD showing interstitial and intra-alveolar oedema, hyaline membranes lining the alveolar septa, necrosis of AECs, hyperplasia of type 2 AECs and perivascular T-cell infiltration [127]. Moreover, pathognomonic changes of COVID-19 seem to be severe EC injuries, *e.g.* disruption of intercellular junctions and loss of contact to the basal membrane. Suggesting a cytopathic effect, these structural changes in ECs were associated with the intracellular presence of the SARS-CoV-2 virus and increased angiotensin converting enzyme 2 expression, the host cell receptor of SARS-CoV-2 virus, on AECs and pulmonary ECs compared to normal lung tissue [127]. Additionally, alveolar capillary microthrombi were significantly more prevalent in COVID-19 lungs compared to lung samples of patients suffering from influenza [127]. Regarding changes of the pulmonary vasculature, both intussusceptive and sprouting angiogenesis were found to be increased [127]. The lungs of COVID-19 patients exhibit distorted vascularity, with deformed and elongated capillaries as well as sudden changes in calibre (figure 2b) [128]. In association with these morphological findings, transcriptomic profiling has revealed altered expression of angiogenesis-related genes (CXCR4 and CXCL12) [129]. With increased hospitalisation time, gene expression analysis on the RNA and protein levels has shown a shift from pro-inflammatory to profibrotic activity, *e.g.* as demonstrated by increased expression of collagen subtypes [130].

In terms of fibrotic remodelling in COVID-19, histological examinations of lung specimens in patients following COVID-19 infection indicate three clusters of post-COVID ILD with different histological patterns: “pre-existing chronic-fibrosing” (cluster 1), “acute/subacute injury” (cluster 2) and “vascular changes” (cluster 3). Cluster 3 is characterised by an increase in vascular size, dilatation and distortion in capillaries and venules, indicative of the crucial role of the pulmonary vasculature in COVID-19 [131]. In addition to the different histological appearance, the pattern of gene expression in COVID-19 also differs from other ILD entities, namely UIP, NSIP and AFE [129]. Based on current knowledge, COVID-19 is likely linked to vascular aetiology and defines a distinct morphomolecular pattern regarding observable pulmonary fibrotic alterations [132].

Current antifibrotic therapy and future targets

The approval of pirfenidone and nintedanib for IPF by the US Food and Drug Administration in 2014 marked a milestone in the therapy of pulmonary fibrosis. Over the following years, nintedanib was then approved for therapy of SSc-ILD and since 2020 it is the current treatment for all forms of progressive pulmonary fibrosis regardless of an idiopathic or secondary cause (figure 5a). The mechanism of action of pirfenidone has not been fully established. Existing data suggest that pirfenidone exerts both antifibrotic and anti-inflammatory properties. Pirfenidone attenuates fibroblast proliferation, production of fibrosis-associated proteins and cytokines, and the increased biosynthesis and accumulation of ECM in response to TGF-β and PDGF [133]. Nintedanib is a multikinase inhibitor including the PDGF receptors α and β, FGF receptors 1–3 and VEGF receptors 1–3. Nintedanib binds competitively to the ATP-binding pocket of these kinases and inhibits the intracellular signalling cascades which have been demonstrated to be involved in the pathogenesis of fibrotic tissue remodelling in ILDs (figure 5b) [133].

It is also noteworthy that the role of angiogenesis and the fibrovascular interface in the progression and development of fibrosis is one that is subject to ambivalence. Thereby, a negative correlation was observed between the extent of fibrosis and vascular capillary density in IPF. On the other hand, an increase in angiostatic factors was noted in UIP and decreased angiogenesis was observed in HP. A significant reduction in microvessel density was observed in SSc-NSIP. The present findings illustrate the heterogeneity in vascular responses within DPLDs but do not establish a direct, uniform link to the underlying fibrotic mechanisms. Nevertheless, if pulmonary fibrosis is considered to be at least partly a vascular-driven disease, targeting the previously described mechanism within the fibrovascular interface could open up new therapeutic strategies.

Looking at the current treatment options from this perspective, there is some evidence that nintedanib affects the microvasculature in IPF. Nintedanib treatment of mice with bleomycin-induced pulmonary fibrosis led to normalisation of the microvasculature as evidenced by a decrease in vessel density, an increase in intervascular distances and a reduction in vessel diameters. At the same time, an improvement in lung function and lung tissue density has been demonstrated [134].

Several new molecular targets have been developed to expand the therapeutic options in ILDs. Based on their signalling pathways, some of them may interact directly or indirectly with the pulmonary microvasculature. Two new compounds and their current status are discussed in the following paragraphs.

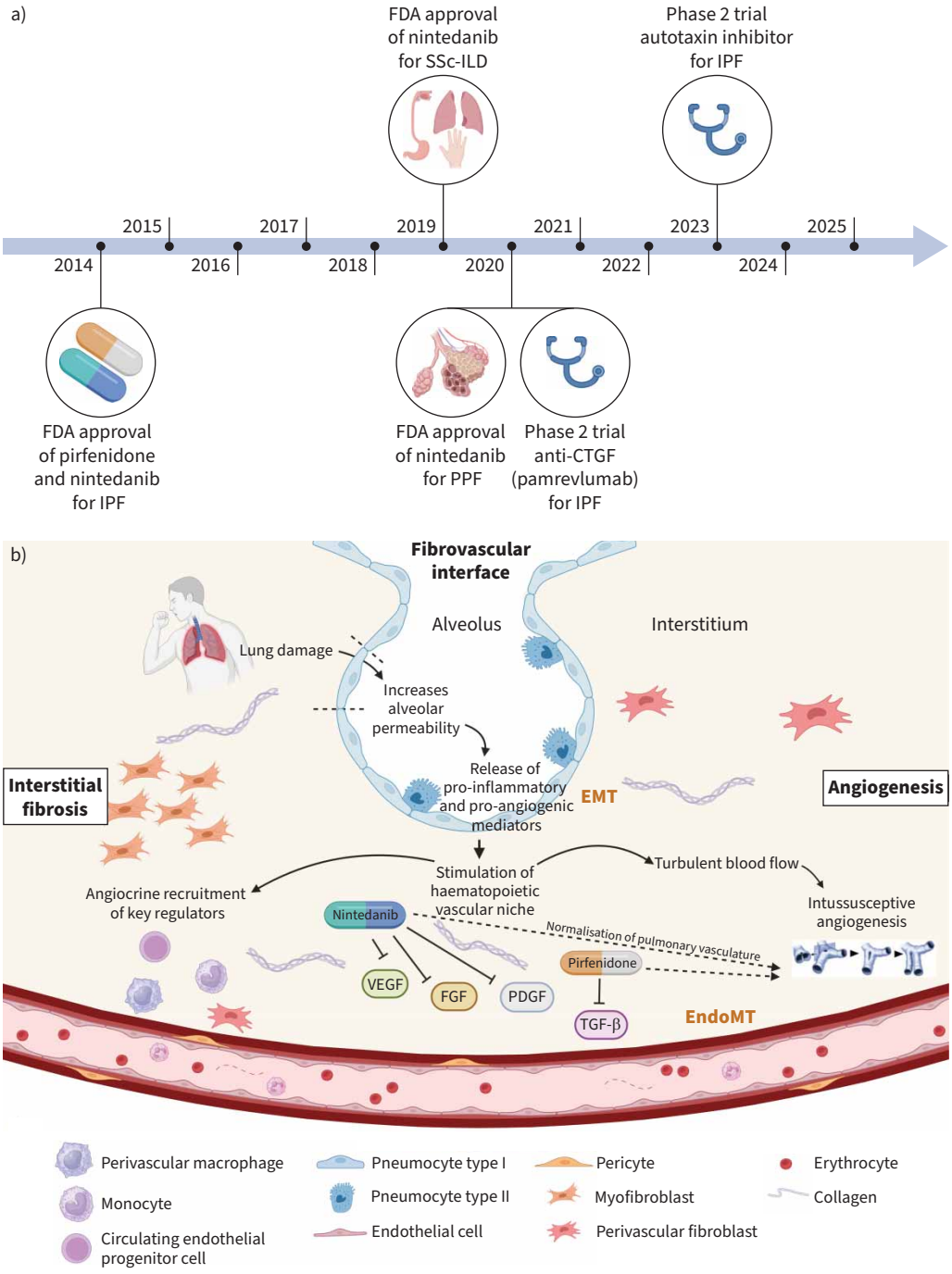


FIGURE 5 a) Pipeline of current antifibrotic treatments and possible therapeutic options in clinical testing. FDA: Food and Drug Administration; SSc: systemic sclerosis; ILD: interstitial lung disease; IPF: idiopathic pulmonary fibrosis; PPF: progressive pulmonary fibrosis; CTGF: connective tissue growth factor. b) Fibrovascular interface and the effect of current antifibrotic treatments. Epithelial–mesenchymal transition (EMT) is based on the alveolar epithelium; endothelial–mesenchymal transition (EndoMT) starts from the endothelium of the capillary vessels. Lung damage leads to increased alveolar permeability. This is followed by release of pro-inflammatory and pro-angiogenic mediators stimulating the haematopoietic vascular niche. A turbulent blood flow promotes intussusceptive angiogenesis, and angiocrine recruitment of key regulators such as perivascular macrophages and perivascular fibroblasts, monocytes and circulating endothelial progenitor cells takes place leading to interstitial fibrosis. Nintedanib inhibits vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF). Pirfenidone is known to block transforming growth factor (TGF)-β, thus leading to normalisation of the vasculature. Figure partially created with BioRender.com.

Pamrevlumab, a human monoclonal antibody, is an inhibitor of CTGF [135]. As a main signal molecule in fibrogenesis, CTGF promotes ECM production and decreases its degradation, mainly based on upregulation of other growth factors such as TGF-β [136]. Considering the vasculature, *in vivo* studies of bleomycin-induced mouse models of pulmonary fibrosis demonstrated elevated CTGF levels in ECs 4 weeks after bleomycin stimulation, possibly contributing to proliferation and activation of fibroblasts [31]. Additionally, overexpression of CTGF was associated with the formation of a proliferative phenotype of ECs of the pulmonary vasculature in bleomycin-treated rats with pulmonary fibrosis [137]. So, as a potential target, treatment with pamrevlumab attenuated IPF progression in a phase 2 trial [135]. Unfortunately, there was no significant difference considering the primary end-point of absolute change in forced vital capacity (FVC) in the ZEPHYRUS-1 clinical trial, a phase 3, double-blind randomised trial [135].

Other more currently investigated targets inhibit the autotaxin (ATX)/LPA axis. The lysophospholipid LPA is incorporated in several physiological processes, such as cellular proliferation, differentiation and cytoskeleton changes, as well as in endothelial permeability [138, 139]. ATX displays an enzyme whose lysophospholipase D activity catalyses the synthesis of LPA [140, 141]. Immunohistochemical analyses of human and mouse lung tissue samples demonstrated elevated ATX concentration in human UIP/IPF and fibrotic NSIP and murine bleomycin-induced pulmonary fibrosis [142]. Based on bleomycin mouse models, Tager *et al*. [143] demonstrated LPA1 receptor and a stronger LPA1 expression on ECs which have shown increased vascular permeability, a driver of fibrogenesis. Thus, the ATX/LPA axis potentially offers several target structures for new therapeutic approaches. After the ATX inhibitor ziritaxestat showed improvement in FVC in a phase 2a trial in a cohort of patients with IPF, the results could not be confirmed in the ISABELA 1 and 2 phase 3 trials [144, 145]. The LPA1 antagonist showed promising results in a phase 2 trial in patients with IPF, indicating a decline in percentage predicted FVC [146]. The results of further clinical studies will be of interest.

Conclusions

In conclusion, morphomolecular aberrations and dynamic cellular interactions within the fibrovascular interface take place in multiple entities of pulmonary fibrosis. While significant progress has been made in understanding fibrotic pathways, the role of the vasculature remains underexplored and often underdiagnosed in each disease-specific context. Directing more attention towards vascular alterations may provide crucial insights into the pathophysiology of ILDs. Investigating the vasculature alongside the fibrovascular interface throughout the development of ILD holds promise for uncovering new molecular targets and advancing therapeutic approaches tailored to the diverse spectrum of these debilitating conditions.

Provenance: Commissioned article, peer reviewed.

Acknowledgement: This work is dedicated to the memory of the late Professor Tobias Welte. "*It is like a voyage of discovery into unknown lands, seeking not for new territory but for new knowledge. It should appeal to those with a good sense of adventure.*" Frederick Sanger (speech at the Nobel Banquet, 10 December 1980; www.nobelprize.org/prizes/chemistry/1980/sanger/speech).

Conflict of interest: All authors have nothing to disclose.

Support statement: Supported by NIH grant HL94567, NHLBI grant HL134229 and Chan Zuckerberg Initiative grant 2020-225394.

References

1 Raghu G, Remy-Jardin M, Richeldi L, *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: e18–e47.
2 Tcherakian C, Cottin V, Brillet P-Y, *et al.* Progression of idiopathic pulmonary fibrosis: lessons from asymmetrical disease. *Thorax* 2011; 66: 226–231.
3 Travis WD, Hunninghake G, Talmadge E, *et al.* Idiopathic nonspecific interstitial pneumonia. *Am J Respir Crit Care Med* 2008; 177: 1338–1347.
4 Nishimura K, Izumi T, Kitaichi M, *et al.* The diagnostic accuracy of high-resolution computed tomography in diffuse infiltrative lung diseases. *Chest* 1993; 104: 1149–1155.
5 Hunninghake GW, Zimmerman MB, Schwartz DA, *et al.* Utility of a lung biopsy for the diagnosis of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2001; 164: 193–196.
6 Zhang Y, Wang J. Cellular and molecular mechanisms in idiopathic pulmonary fibrosis. *Adv Respir Med* 2023; 91: 26–48.

7 Maher TM. Interstitial lung disease: a review. *JAMA* 2024; 331: 1655–1665.
8 Flaherty KR, Martinez FJ, Travis W, *et al.* Nonspecific interstitial pneumonia (NSIP). *Semin Respir Crit Care Med* 2001; 22: 423–434.
9 Travis WD, Matsui K, Moss J, *et al.* Idiopathic nonspecific interstitial pneumonia: prognostic significance of cellular and fibrosing patterns: survival comparison with usual interstitial pneumonia and desquamative interstitial pneumonia. *Am J Surg Pathol* 2000; 24: 19–33.
10 Raghu G, Remy-Jardin M, Myers JL, *et al.* Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med* 2018; 198: e44–e68.
11 Troy LK, Grainge C, Corte TJ, *et al.* Diagnostic accuracy of transbronchial lung cryobiopsy for interstitial lung disease diagnosis (COLDICE): a prospective, comparative study. *Lancet Respir Med* 2020; 8: 171–181.
12 Croasdell Lucchini A, Gachanja NN, Rossi AG, *et al.* Epithelial cells and inflammation in pulmonary wound repair. *Cells* 2021; 10: 339.
13 Yang J, Pan X, Wang L, *et al.* Alveolar cells under mechanical stressed niche: critical contributors to pulmonary fibrosis. *Mol Med* 2020; 26: 95.
14 Kato M, Takahashi F, Sato T, *et al.* Tranilast inhibits pulmonary fibrosis by suppressing TGFβ/SMAD2 pathway. *Drug Des Devel Ther* 2020; 14: 4593–4603.
15 Crosby LM, Waters CM. Epithelial repair mechanisms in the lung. *Am J Physiol Lung Cell Mol Physiol* 2010; 298: L715–L731.
16 Wilson MS, Wynn TA. Pulmonary fibrosis: pathogenesis, etiology and regulation. *Mucosal Immunol* 2009; 2: 103–121.
17 Kramann R, DiRocco DP, Humphreys BD. Understanding the origin, activation and regulation of matrix-producing myofibroblasts for treatment of fibrotic disease. *J Pathol* 2013; 231: 273–289.
18 Wynn TA. Integrating mechanisms of pulmonary fibrosis. *J Exp Med* 2011; 208: 1339–1350.
19 Yue X, Shan B, Lasky JA. TGF-β: titan of lung fibrogenesis. *Curr Enzym Inhib* 2010; 6: 67–77.
20 Scotton CJ, Chambers RC. Molecular targets in pulmonary fibrosis: the myofibroblast in focus. *Chest* 2007; 132: 1311–1321.
21 Hinz B, Phan SH, Thannickal VJ, *et al.* The myofibroblast: one function, multiple origins. *Am J Pathol* 2007; 170: 1807–1816.
22 Broekelmann TJ, Limper AH, Colby TV, *et al.* Transforming growth factor beta 1 is present at sites of extracellular matrix gene expression in human pulmonary fibrosis. *Proc Natl Acad Sci USA* 1991; 88: 6642–6646.
23 Sime PJ, Xing Z, Graham FL, *et al.* Adenovector-mediated gene transfer of active transforming growth factor-beta1 induces prolonged severe fibrosis in rat lung. *J Clin Invest* 1997; 100: 768–776.
24 Maeda A, Hiyama K, Yamakido H, *et al.* Increased expression of platelet-derived growth factor A and insulin-like growth factor-I in BAL cells during the development of bleomycin-induced pulmonary fibrosis in mice. *Chest* 1996; 109: 780–786.
25 Fehrenbach H, Haase M, Kasper M, *et al.* Alterations in the immunohistochemical distribution patterns of vascular endothelial growth factor receptors Flk1 and Flt1 in bleomycin-induced rat lung fibrosis. *Virchows Archiv* 1999; 435: 20–31.
26 MacKenzie B, Korfei M, Henneke I, *et al.* Increased FGF1-FGFRc expression in idiopathic pulmonary fibrosis. *Respir Res* 2015; 16: 83.
27 Alsafadi HN, Staab-Weijnitz CA, Lehmann M, *et al.* An *ex vivo* model to induce early fibrosis-like changes in human precision-cut lung slices. *Am J Physiol Lung Cell Mol Physiol* 2017; 312: L896–L902.
28 Peng R, Sridhar S, Tyagi G, *et al.* Bleomycin induces molecular changes directly relevant to idiopathic pulmonary fibrosis: a model for “active” disease. *PLoS One* 2013; 8: e59348.
29 Jonigk D, Stark H, Braubach P, *et al.* Morphological and molecular motifs of fibrosing pulmonary injury patterns. *J Pathol Clin Res* 2019; 5: 256–271.
30 Epstein Shochet G, Brook E, Israeli-Shani L, *et al.* Fibroblast paracrine TNF-α signaling elevates integrin A5 expression in idiopathic pulmonary fibrosis (IPF). *Respir Res* 2017; 18: 122.
31 Leach HG, Chrobak I, Han R, *et al.* Endothelial cells recruit macrophages and contribute to a fibrotic milieu in bleomycin lung injury. *Am J Respir Cell Mol Biol* 2013; 49: 1093–1101.
32 Reyfman PA, Walter JM, Joshi N, *et al.* Single-cell transcriptomic analysis of human lung provides insights into the pathobiology of pulmonary fibrosis. *Am J Respir Crit Care Med* 2019; 199: 1517–1536.
33 Long H, Lichtnekert J, Andrassy J, *et al.* Macrophages and fibrosis: how resident and infiltrating mononuclear phagocytes account for organ injury, regeneration or atrophy. *Front Immunol* 2023; 14: 1194988.
34 van Geffen C, Deißler A, Quante M, *et al.* Regulatory immune cells in idiopathic pulmonary fibrosis: friends or foes? *Front Immunol* 2021; 12: 663203.
35 Kamiya M, Carter H, Espindola MS, *et al.* Immune mechanisms in fibrotic interstitial lung disease. *Cell* 2024; 187: 3506–3530.
36 Obayashi Y, Yamadori I, Fujita J, *et al.* The role of neutrophils in the pathogenesis of idiopathic pulmonary fibrosis. *Chest* 1997; 112: 1338–1343.

37 Gregory AD, Kliment CR, Metz HE, *et al.* Neutrophil elastase promotes myofibroblast differentiation in lung fibrosis. *J Leukoc Biol* 2015; 98: 143–152.
38 Chrysanthopoulou A, Mitroulis I, Apostolidou E, *et al.* Neutrophil extracellular traps promote differentiation and function of fibroblasts. *J Pathol* 2014; 233: 294–307.
39 Suzuki T, Karayama M, Aoshima Y, *et al.* Association of the lung immune prognostic index with the survival of patients with idiopathic interstitial pneumonias. *Respirology* 2024; 29: 136–145.
40 Suzuki Y, Kono M, Hasegawa H, *et al.* Neutrophil–lymphocyte ratio in patients with idiopathic pleuroparenchymal fibroelastosis. *BMJ Open Respir Res* 2023; 10: e001763.
41 Aird WC. Phenotypic heterogeneity of the endothelium. *Circ Res* 2007; 100: 174–190.
42 Schupp JC, Adams TS, Cosme C Jr, *et al.* Integrated single-cell atlas of endothelial cells of the human lung. *Circulation* 2021; 144: 286–302.
43 Gillich A, Zhang F, Farmer CG, *et al.* Capillary cell-type specialization in the alveolus. *Nature* 2020; 586: 785–789.
44 Turner-Warwick M. Precapillary systemic-pulmonary anastomoses. *Thorax* 1963; 18: 225–237.
45 Takabatake N, Arao T, Sata M, *et al.* Involvement of pulmonary endothelial cell injury in the pathogenesis of pulmonary fibrosis: clinical assessment by ^{123}I-MIBG lung scintigraphy. *Eur J Nucl Med Mol Imaging* 2005; 32: 221–228.
46 Kato S, Inui N, Hakamata A, *et al.* Changes in pulmonary endothelial cell properties during bleomycin-induced pulmonary fibrosis. *Respir Res* 2018; 19: 127.
47 Zhang L, Gao S, White Z, *et al.* Single-cell transcriptomic profiling of lung endothelial cells identifies dynamic inflammatory and regenerative subpopulations. *JCI Insight* 2022; 7: e158079.
48 Peled A, Grabovsky V, Habler L, *et al.* The chemokine SDF-1 stimulates integrin-mediated arrest of CD34$^+$ cells on vascular endothelium under shear flow. *J Clin Invest* 1999; 104: 1199–1211.
49 Ribatti D, Crivellato E. "Sprouting angiogenesis", a reappraisal. *Dev Biol* 2012; 372: 157–165.
50 Jakobsson L, Franco CA, Bentley K, *et al.* Endothelial cells dynamically compete for the tip cell position during angiogenic sprouting. *Nat Cell Biol* 2010; 12: 943–953.
51 Eilken HM, Adams RH. Dynamics of endothelial cell behavior in sprouting angiogenesis. *Curr Opin Cell Biol* 2010; 22: 617–625.
52 Lapenna A, De Palma M, Lewis CE. Perivascular macrophages in health and disease. *Nat Rev Immunol* 2018; 18: 689–702.
53 Hashimoto N, Phan SH, Imaizumi K, *et al.* Endothelial–mesenchymal transition in bleomycin-induced pulmonary fibrosis. *Am J Respir Cell Mol Biol* 2010; 43: 161–172.
54 May J, Mitchell JA, Jenkins RG. Beyond epithelial damage: vascular and endothelial contributions to idiopathic pulmonary fibrosis. *J Clin Invest* 2023; 133: e172058.
55 Shepro D, Morel NML. Pericyte physiology. *FASEB J* 1993; 7: 1031–1038.
56 Rowley JE, Johnson JR. Pericytes in chronic lung disease. *Int Arch Allergy Immunol* 2014; 164: 178–188.
57 Sava P, Ramanathan A, Dobronyi A, *et al.* Human pericytes adopt myofibroblast properties in the microenvironment of the IPF lung. *JCI Insight* 2017; 2: e96352.
58 Burri PH, Hlushchuk R, Djonov V. Intussusceptive angiogenesis: its emergence, its characteristics, and its significance. *Dev Dyn* 2004; 231: 474–488.
59 Dudley AC, Griffioen AW. The modes of angiogenesis: an updated perspective. *Angiogenesis* 2023; 26: 477–480.
60 Ackermann M, Mentzer SJ, Kolb M, *et al.* Inflammation and intussusceptive angiogenesis in COVID-19: everything in and out of flow. *Eur Respir J* 2020; 56: 2003147.
61 Gerhardt H, Golding M, Fruttiger M, *et al.* VEGF guides angiogenic sprouting utilizing endothelial tip cell filopodia. *J Cell Biol* 2003; 161: 1163–1177.
62 Ackermann M, Houdek JP, Gibney BC, *et al.* Sprouting and intussusceptive angiogenesis in postpneumonectomy lung growth: mechanisms of alveolar neovascularization. *Angiogenesis* 2014; 17: 541–551.
63 Mentzer SJ, Konerding MA. Intussusceptive angiogenesis: expansion and remodeling of microvascular networks. *Angiogenesis* 2014; 17: 499–509.
64 Burri PH, Tarek MR. A novel mechanism of capillary growth in the rat pulmonary microcirculation. *Anat Rec* 1990; 228: 35–45.
65 Djonov V, Baum O, Burri PH. Vascular remodeling by intussusceptive angiogenesis. *Cell Tissue Res* 2003; 314: 107–117.
66 Konerding MA, Turhan A, Ravnic DJ, *et al.* Inflammation-induced intussusceptive angiogenesis in murine colitis. *Anat Rec* 2010; 293: 849–857.
67 Gomez-Salinero JM, Rafii S. Endothelial cell adaptation in regeneration. *Science* 2018; 362: 1116–1117.
68 Psaltis PJ, Simari RD. Vascular wall progenitor cells in health and disease. *Circ Res* 2015; 116: 1392–1412.
69 Keighron C, Lyons CJ, Creane M, *et al.* Recent advances in endothelial progenitor cells toward their use in clinical translation. *Front Med* 2018; 5: 354.

70 Smadja DM. Vasculogenic stem and progenitor cells in human: future cell therapy product or liquid biopsy for vascular disease. *Adv Exp Med Biol* 2019; 1201: 215–237.
71 Asahara T, Murohara T, Sullivan A, *et al.* Isolation of putative progenitor endothelial cells for angiogenesis. *Science* 1997; 275: 964–967.
72 Yoder MC, Mead LE, Prater D, *et al.* Redefining endothelial progenitor cells via clonal analysis and hematopoietic stem/progenitor cell principals. *Blood* 2007; 109: 1801–1809.
73 Ng CY, Cheung C. Origins and functional differences of blood endothelial cells. *Semin Cell Dev Biol* 2024; 155: 23–29.
74 Smadja D, Dorfmüller P, Guerin C, *et al.* Cooperation between human fibrocytes and endothelial colony-forming cells increases angiogenesis via the CXCR4 pathway. *Thromb Haemost* 2017; 112: 1002–1013.
75 Smadja DM, Rossi E, Haviari S, *et al.* Thrombin receptor PAR1 silencing in endothelial colony-forming cells modifies stemness and vasculogenic properties. *J Thromb Haemost* 2023; 21: 3640–3648.
76 Dragoni S, Laforenza U, Bonetti E, *et al.* Vascular endothelial growth factor stimulates endothelial colony forming cells proliferation and tubulogenesis by inducing oscillations in intracellular Ca^{2+} concentration. *Stem Cells* 2011; 29: 1898–1907.
77 Evrard SM, d'Audigier C, Mauge L, *et al.* The profibrotic cytokine transforming growth factor-β1 increases endothelial progenitor cell angiogenic properties. *J Thromb Haemost* 2012; 10: 670–679.
78 Cras A, Larghero J, Rossi E, *et al.* Nestin is a new partner in endothelial colony forming cell angiogenic potential. *Stem Cell Rev Rep* 2023; 19: 2541–2550.
79 Benslimane-Ahmim Z, Heymann D, Dizier B, *et al.* Osteoprotegerin, a new actor in vasculogenesis, stimulates endothelial colony-forming cells properties. *J Thromb Haemost* 2011; 9: 834–843.
80 Alphonse RS, Vadivel A, Fung M, *et al.* Existence, functional impairment, and lung repair potential of endothelial colony-forming cells in oxygen-induced arrested alveolar growth. *Circulation* 2014; 129: 2144–2157.
81 Paschalaki KE, Randi AM. Recent advances in endothelial colony forming cells toward their use in clinical translation. *Front Med* 2018; 5: 295.
82 Gouzi F, Philippe A, Blervaque L, *et al.* Plasma ratio of angiopoietin-2 to angiopoietin-1 is a biomarker of vascular impairment in chronic obstructive pulmonary disease patients. *Angiogenesis* 2022; 25: 275–277.
83 Smadja DM, Mauge L, Nunes H, *et al.* Imbalance of circulating endothelial cells and progenitors in idiopathic pulmonary fibrosis. *Angiogenesis* 2013; 16: 147–157.
84 Billoir P, Blandinières A, Gendron N, *et al.* Endothelial colony-forming cells from idiopathic pulmonary fibrosis patients have a high procoagulant potential. *Stem Cell Rev Rep* 2021; 17: 694–699.
85 Blandinières A, Gendron N, Bacha N, *et al.* Interleukin-8 release by endothelial colony-forming cells isolated from idiopathic pulmonary fibrosis patients might contribute to their pathogenicity. *Angiogenesis* 2019; 22: 325–339.
86 Benyamine A, Magalon J, Cointe S, *et al.* Increased serum levels of fractalkine and mobilisation of $CD34^{+}CD45^{-}$ endothelial progenitor cells in systemic sclerosis. *Arthritis Res Ther* 2017; 19: 60.
87 Raghu G, Collard HR, Egan JJ, *et al.* An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2011; 183: 788–824.
88 American Thoracic Society/European Respiratory Society. American Thoracic Society/European Respiratory Society international multidisciplinary consensus classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med* 2002; 165: 277–304.
89 Ebina M, Shimizukawa M, Shibata N, *et al.* Heterogeneous increase in CD34-positive alveolar capillaries in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2004; 169: 1203–1208.
90 Cosgrove GP, Brown KK, Schiemann WP, *et al.* Pigment epithelium-derived factor in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2004; 170: 242–251.
91 Ackermann M, Stark H, Neubert L, *et al.* Morphomolecular motifs of pulmonary neoangiogenesis in interstitial lung diseases. *Eur Respir J* 2020; 55: 1900933.
92 Adams TS, Schupp JC, Poli S, *et al.* Single-cell RNA-seq reveals ectopic and aberrant lung-resident cell populations in idiopathic pulmonary fibrosis. *Sci Adv* 2020; 6: eaba1983.
93 Gaikwad AV, Lu W, Dey S, *et al.* Vascular remodelling in idiopathic pulmonary fibrosis patients and its detrimental effect on lung physiology: potential role of endothelial-to-mesenchymal transition. *ERJ Open Res* 2022; 8: 00571-2021.
94 Neubert L, Borchert P, Stark H, *et al.* Molecular profiling of vascular remodeling in chronic pulmonary disease. *Am J Pathol* 2020; 190: 1382–1396.
95 Bian F, Lan YW, Zhao S, *et al.* Lung endothelial cells regulate pulmonary fibrosis through FOXF1/R-Ras signaling. *Nat Commun* 2023; 14: 2560.
96 Länger F, Stark H, Braubach P, *et al.* Schädigungsmuster interstitieller Lungenerkrankungen. [Injury patterns in interstitial lung diseases.] *Pathologe* 2018; 39: 262–271.
97 Katzenstein A-LA, Fiorelli RF. Nonspecific interstitial pneumonia/fibrosis: histologic features and clinical significance. *Am J Surg Pathol* 1994; 18: 136–147.

98 Travis WD, Costabel U, Hansell DM, *et al.* An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med* 2013; 188: 733–748.

99 Wandel E, Saalbach A, Sittig D, *et al.* Thy-1 (CD90) is an interacting partner for CD97 on activated endothelial cells. *J Immunol* 2012; 188: 1442–1450.

100 Wnuk M, Hlushchuk R, Tuffin G, *et al.* The effects of PTK787/ZK222584, an inhibitor of VEGFR and PDGFRβ pathways, on intussusceptive angiogenesis and glomerular recovery from Thy1.1 nephritis. *Am J Pathol* 2011; 178: 1899–1912.

101 Schupp JC, Manning EP, Chioccioli M, *et al.* Alveolar vascular remodeling in nonspecific interstitial pneumonia: replacement of normal lung capillaries with COL15A1-positive endothelial cells. *Am J Respir Crit Care Med* 2023; 208: 819–822.

102 Ofek E, Sato M, Saito T, *et al.* Restrictive allograft syndrome post lung transplantation is characterized by pleuroparenchymal fibroelastosis. *Mod Pathol* 2013; 26: 350–356.

103 Takeuchi Y, Miyagawa-Hayashino A, Chen F, *et al.* Pleuroparenchymal fibroelastosis and non-specific interstitial pneumonia: frequent pulmonary sequelae of haematopoietic stem cell transplantation. *Histopathology* 2015; 66: 536–544.

104 Enomoto Y, Nakamura Y, Colby TV, *et al.* Radiologic pleuroparenchymal fibroelastosis-like lesion in connective tissue disease-related interstitial lung disease. *PLoS One* 2017; 12: e0180283.

105 Jonigk D, Rath B, Borchert P, *et al.* Comparative analysis of morphological and molecular motifs in bronchiolitis obliterans and alveolar fibroelastosis after lung and stem cell transplantation. *J Pathol Clin Res* 2017; 3: 17–28.

106 Frankel SK, Cool CD, Lynch DA, *et al.* Idiopathic pleuroparenchymal fibroelastosis: description of a novel clinicopathologic entity. *Chest* 2004; 126: 2007–2013.

107 von der Thusen JH. Pleuroparenchymal fibroelastosis: its pathological characteristics. *Curr Respir Med Rev* 2013; 9: 238–247.

108 Braubach P, Werlein C, Verleden SE, *et al.* Pulmonary fibroelastotic remodelling revisited. *Cells* 2021; 10: 1362.

109 Kinoshita Y, Ishii H, Kushima H, *et al.* Remodeling of the pulmonary artery in idiopathic pleuroparenchymal fibroelastosis. *Sci Rep* 2020; 10: 306.

110 Selman M, Buendía-Roldán I, Navarro C, *et al.* Hypersensitivity pneumonitis. *In:* Baughman R, Carbone R, Nathan S, eds. Pulmonary Hypertension and Interstitial Lung Disease. Cham, Springer, 2017; pp. 145–164.

111 Pérez ERF, Swigris JJ, Forssén AV, *et al.* Identifying an inciting antigen is associated with improved survival in patients with chronic hypersensitivity pneumonitis. *Chest* 2013; 144: 1644–1651.

112 De Sadeleer LJ, Hermans F, De Dycker E, *et al.* Effects of corticosteroid treatment and antigen avoidance in a large hypersensitivity pneumonitis cohort: a single-centre cohort study. *J Clin Med* 2018; 8: 14.

113 Coleman A, Colby TV. Histologic diagnosis of extrinsic allergic alveolitis. *Am J Surg Pathol* 1988; 12: 514–518.

114 Raghu G, Remy-Jardin M, Ryerson CJ, *et al.* Diagnosis of hypersensitivity pneumonitis in adults: an official ATS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med* 2020; 202: e36–e69.

115 Churg A, Bilawich A, Wright JL. Pathology of chronic hypersensitivity pneumonitis. What is it? What are the diagnostic criteria? Why do we care? *Arch Pathol Lab Med* 2017; 142: 109–119.

116 De Sadeleer LJ, McDonough JE, Schupp JC, *et al.* Lung microenvironments and disease progression in fibrotic hypersensitivity pneumonitis. *Am J Respir Crit Care Med* 2022; 205: 60–74.

117 Desai SR, Veeraraghavan S, Hansell DM, *et al.* CT features of lung disease in patients with systemic sclerosis: comparison with idiopathic pulmonary fibrosis and nonspecific interstitial pneumonia. *Radiology* 2004; 232: 560–567.

118 Solomon JJ, Olson AL, Fischer A, *et al.* Scleroderma lung disease. *Eur Respir Rev* 2013; 22: 6–19.

119 Bouros D, Wells AU, Nicholson AG, *et al.* Histopathologic subsets of fibrosing alveolitis in patients with systemic sclerosis and their relationship to outcome. *Am J Respir Crit Care Med* 2002; 165: 1581–1586.

120 Franco de Carvalho E, Parra ER, de Souza R, *et al.* Parenchymal and vascular interactions in the pathogenesis of nonspecific interstitial pneumonia in systemic sclerosis and idiopathic interstitial pneumonia. *Respiration* 2007; 76: 146–153.

121 Mendoza FA, Piera-Velazquez S, Farber JL, *et al.* Endothelial cells expressing endothelial and mesenchymal cell gene products in lung tissue from patients with systemic sclerosis-associated interstitial lung disease. *Arthritis Rheumatol* 2016; 68: 210–217.

122 Zhou S, Wang Y, Zhu T, *et al.* CT features of coronavirus disease 2019 (COVID-19) pneumonia in 62 patients in Wuhan, China. *AJR Am J Roentgenol* 2020; 214: 1287–1294.

123 Meyer NJ, Gattinoni L, Calfee CS. Acute respiratory distress syndrome. *Lancet* 2021; 398: 622–637.

124 Castro CY. ARDS and diffuse alveolar damage: a pathologist's perspective. *Semin Thorac Cardiovasc Surg* 2006; 18: 13–19.

125 Thille AW, Esteban A, Fernández-Segoviano P, *et al.* Chronology of histological lesions in acute respiratory distress syndrome with diffuse alveolar damage: a prospective cohort study of clinical autopsies. *Lancet Respir Med* 2013; 1: 395–401.

126 Tomashefski JF Jr, Davies P, Boggis C, *et al.* The pulmonary vascular lesions of the adult respiratory distress syndrome. *Am J Pathol* 1983; 112: 112–126.

127 Ackermann M, Verleden SE, Kuehnel M, *et al.* Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. *N Engl J Med* 2020; 383: 120–128.

128 Mentzer SJ, Ackermann M, Jonigk D. Endothelialitis, microischemia, and intussusceptive angiogenesis in COVID-19. *Cold Spring Harb Perspect Med* 2022; 12: a041157.

129 Ackermann M, Kamp JC, Werlein C, *et al.* The fatal trajectory of pulmonary COVID-19 is driven by lobular ischemia and fibrotic remodelling. *EBioMedicine* 2022; 85: 104296.

130 Kamp JC, Neubert L, Ackermann M, *et al.* Time-dependent molecular motifs of pulmonary fibrogenesis in COVID-19. *Int J Mol Sci* 2022; 23: 1583.

131 Ravaglia C, Doglioni C, Chilosi M, *et al.* Clinical, radiological and pathological findings in patients with persistent lung disease following SARS-CoV-2 infection. *Eur Respir J* 2022; 60: 2102411.

132 Kamp JC, Werlein C, Plucinski EKJ, *et al.* Novel insight into pulmonary fibrosis and long COVID. *Am J Respir Crit Care Med* 2023; 207: 1105–1107.

133 Noble PW, Albera C, Bradford WZ, *et al.* Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. *Lancet* 2011; 377: 1760–1769.

134 Ackermann M, Kim YO, Wagner WL, *et al.* Effects of nintedanib on the microvascular architecture in a lung fibrosis model. *Angiogenesis* 2017; 20: 359–372.

135 Raghu G, Richeldi L, Fernández Pérez ER, *et al.* Pamrevlumab for idiopathic pulmonary fibrosis: the ZEPHYRUS-1 randomized clinical trial. *JAMA* 2024; 332: 380–389.

136 Raghu G, Scholand MB, de Andrade 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: 1481–1491.

137 Yan L-F, Wei Y-N, Nan H-Y, *et al.* Proliferative phenotype of pulmonary microvascular endothelial cells plays a critical role in the overexpression of CTGF in the bleomycin-injured rat. *Exp Toxicol Pathol* 2014; 66: 61–71.

138 Tran KC, Zhao J. Lysophosphatidic acid regulates Rho family of GTPases in lungs. *Cell Biochem Biophys* 2021; 79: 493–496.

139 Alioli C, Demesmay L, Peyruchaud O, *et al.* Autotaxin/lysophosphatidic acid axis: from bone biology to bone disorders. *Int J Mol Sci* 2022; 23: 3427.

140 Ninou I, Magkrioti C, Aidinis V. Autotaxin in pathophysiology and pulmonary fibrosis. *Front Med* 2018; 5: 180.

141 Yung YC, Stoddard NC, Chun J. LPA receptor signaling: pharmacology, physiology, and pathophysiology. *J Lipid Res* 2014; 55: 1192–1214.

142 van Meeteren LA, Moolenaar WH. Regulation and biological activities of the autotaxin–LPA axis. *Prog Lipid Res* 2007; 46: 145–160.

143 Tager AM, LaCamera P, Shea BS, *et al.* The lysophosphatidic acid receptor LPA1 links pulmonary fibrosis to lung injury by mediating fibroblast recruitment and vascular leak. *Nat Med* 2008; 14: 45–54.

144 Maher TM, van der Aar EM, Van de Steen O, *et al.* Safety, tolerability, pharmacokinetics, and pharmacodynamics of GLPG1690, a novel autotaxin inhibitor, to treat idiopathic pulmonary fibrosis (FLORA): a phase 2a randomised placebo-controlled trial. *Lancet Respir Med* 2018; 6: 627–635.

145 Maher TM, Ford P, Brown KK, *et al.* Ziritaxestat, a novel autotaxin inhibitor, and lung function in idiopathic pulmonary fibrosis: the ISABELA 1 and 2 randomized clinical trials. *JAMA* 2023; 329: 1567–1578.

146 Corte T, Cottin V, Glassberg M, *et al.* BMS-986278, an oral lysophosphatidic acid receptor 1 (LPA1) antagonist, for patients with idiopathic pulmonary fibrosis: results from a phase 2 randomized trial. *Am J Respir Crit Care Med* 2023; 207: A2785.