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Precision medicine in idiopathic pulmonary fibrosis therapy: From translational research to patient-centered care

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Abstract

Idiopathic pulmonary fibrosis (IPF) is a progressive, irreversible fibrotic chronic lung disease affecting predominantly older adults, with a history of smoking. The current model of disease natural course is that recurrent injury of the alveolar epithelium in the context of advanced aging/cellular senescence is followed by defective re-epithelialization and scar tissue formation. Currently, two drugs, nintedanib and pirfenidone, that modify disease progression have been approved worldwide for the treatment of IPF. However, despite treatment, patients with IPF are not cured, and eventually, disease advances in most treated patients. Enhancing biogenomic and metabolic research output, its translation into clinical precision and optimal service delivery through patient-centeredness are key elements to support effective IPF care. In this review, we summarize therapeutic options currently investigated for IPF based on the major pathogenetic pathways and molecular targets that drive pulmonary fibrosis.

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive, irreversible fibrotic chronic lung disease that affects an increasing number of individuals across Europe and North America, with an incidence of three to nine cases per 100000 persons per year [1,2]. The prevalence has been reported as high as 45–199 per 100000 persons in individuals aged 60 to 79 years [3]. The median survival is 3–4 years after diagnosis [4]. IPF occurs primarily in older adults, with a median age at diagnosis of 66 years, a history of smoking and/or genetic variants linked to the disease [5–7].

Currently, two drugs (nintedanib and pirfenidone) have been approved worldwide for the treatment of IPF, on the basis of their efficacy in slowing disease progression, with the use of both as 'conditionally recommended' in the 2015 American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/Latin American Thoracic Society (ALAT) guidelines [8]. Nintedanib reduces disease progression by slowing the rate of decline in forced vital capacity (FVC) with an estimate of a 5-year increase in survival, whereas the side effect profile is characterized mainly by gastrointestinal adverse events [9,10]. Pirfenidone, similar to nintedanib, reduced the proportion of patients exhibiting an FVC decline of $\geq$10% by 48% as assessed in four randomized, placebo-controlled phase 3 studies, with most prominent side effects being gastrointestinal and photosensitivity reactions [11].

However, despite treatment, patients with IPF are not cured, and eventually, disease progresses in most treated patients, with lung transplantation being available only for a restricted minority of patients; moreover, the adverse events of both drugs can lead to treatment discontinuation without the availability of any other pharmacological strategy. The need for a definite cure of

IPF therefore remains. In this review, we summarize major pathogenetic pathways and targets identified over the last years and the corresponding therapeutic options currently investigated for the treatment of IPF.

Pathogenetic pathways in IPF

Pathogenetic pathways in IPF are complex and interconnected, with various abnormalities in the lungs leading to the development of the disease [12]. IPF pathogenesis is centered around type II alveolar epithelial cell dysfunction, coupled to aberrant wound healing cycles, leading to excess extracellular matrix (ECM) production, abnormal re-epithelization of alveoli, and ectopic bronchiolarization, eventually resulting in accumulation of scar tissue, stiffening of the lungs, deterioration of lung function, and death [12,13]. The cellular landscape of the fibrotic lung was recently described with prominent features such as the presence of abnormal basaloid epithelial cells, persistence of myofibroblasts, novel profibrotic macrophage subtypes, and ectopic peribronchial endothelial cells [14].

Although a common dominant underlying cause of IPF has not been identified, risk factors associated with the disease are as follows: mutations that affect the maintenance of telomeres, leading to accelerated aging [15]; mutations in surfactant proteins, leading to Endoplasmic Reticulum (ER) stress [16]; and age- and smoking-related defective proteostasis, leading to defective autophagy and mitophagy, aggregation of misfolded proteins, endoplasmic reticulum stress, mitochondrial dysfunction, and oxidative stress [17,18]. Aberrant activation of type II epithelial cells is a major cause of fibroblast migration, proliferation, and activation, with subsequent exaggerated ECM accumulation and destruction of the lung parenchyma due to the production of profibrotic mediators [19]. Fibroblast aberrant activation and senescence with proinflammatory cytokine production (senescence-associated secretory phenotype), elevated Reactive Oxygen Species (ROS) levels, and myofibroblast persistence are also prominent features of the fibrotic lung [20].

The innate and adaptive immune systems are also involved in the pathogenesis of IPF, although their role is less clearly defined [21]. Macrophages are the most abundant immune cells in the lung, and they play important roles in tissue remodeling during pulmonary fibrosis [22]. Macrophages produce profibrotic mediators such as transforming growth factor β (TGF-β) and platelet-derived growth factor, directly orchestrating the activation of fibroblast functions which are implicated in the aberrant wound-healing cascade during fibrosis [23]. Fibrocytes are a minor fraction of circulating leukocytes that portray a dual phenotype of monocytes (CD34, CD45, CD11b) and fibroblasts (collagens I and III and fibronectin) [24]. Single-cell RNA-Seq analyses of the airway cell population from human lungs have revealed a plethora of cell entities with monocyte and macrophage markers that is reshaping the field of macrophage/monocyte biology, revealing that lung macrophage populations shift in lung fibrosis toward distinct entities with yet uncharacterized functions [25].

Furthermore, the detrimental effects of corticosteroid treatments in IPF may reflect a dominant role of macrophages/monocytes in IPF pathogenesis. Human macrophages matured in the presence of the glucocorticoid fluticasone propionate had decreased expression of MHC class II and costimulatory molecules, but showed increased expression of chemokines promoting monocyte attraction and enhancement of their innate immune functions [26]. Alveolar macrophages derived from recruited monocytes in the bleomycin mouse model contribute significantly to lung fibrosis [22], while macrophage-derived TGF-β plays a dominant role in the development of lung fibrosis [27].

An interplay between mutations in innate immune genes such as MUC5b [28] and TOLLIP [29] and the host response to microbes is a novel pathogenetic axis recognized in IPF. Increased bacterial burden is observed in IPF [30], and microbial peptides have been directly linked to acute exacerbations [31]. The lung microbiome is probably associated with host susceptibility factors owing to either genetic or environmental cues and provides a previously underestimated treatment target [32].

IPF therapeutic targets from basic and translational research

The pathogenic mechanisms leading to irreversible fibrosis are not fully understood; however, advances in basic and translational research have identified new potential therapeutic targets and several molecular pathways that have been strongly associated with the disease, leading to a large number of randomized controlled trials. Currently active phase 2 and 3 trials are summarized in Table 1, and several excellent reviews focusing on the treatment of IPF have been published in the last years after an explosion of novel therapeutics to be tested in IPF [5,11,33–40].

Antifibrotics: targeting mediators of fibroblast activity

Certain molecular pathways have been strongly linked to the disease such as activation of fibroblasts and fibrocytes, via profibrotic mediators secreted by the damaged epithelium. Targeting of the secreted mediators or their signaling has been the basis of several antifibrotic therapies either approved or under investigation. Fibroblast subtypes have been the effector cells primarily and most successfully targeted to date by antifibrotic therapies. Nintedanib, a tyrosine kinase

Table 1

Active clinical studies in phases 2 or 3.

Target molecule	Agent (company)	Acronym	Phase	ClinicalTrials.gov identifier
Connective tissue growth factor	Pamrevlumab (FibroGen)	Zephyrus II	3	NCT04419558
		FGCL-3019-091	3	NCT03955146
Autotaxin	GLPG1690 (Galápagos NV)	ISABELA I	3	NCT03711162
		ISABELA II	3	NCT03733444
Recombinant human pentraxin 2	PRM-151-rhPTX-2 (Hoffmann-La Roche)		3	NCT04594707
				NCT04552899
Galectin-3	TD139 (Galecto Biotech AB)	GALACTIC-1	2b	NCT03832946
G protein–coupled receptor 40 agonist	GLPG1205 (Galápagos NV)		2[a]	NCT03725852
Nrf2	Bardoxolone methyl (Reata Pharmaceuticals)		2[a]	NCT02036970
Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX 1/4) isoforms	GKT137831-Setanaxib		2	NCT03865927
B-cell activating factor receptor	VAY736 (Novartis Pharmaceuticals)		2	NCT03287414
LPA receptor	BMS-986278 (Bristol Myers Squibb)		2	NCT04308681
Heat shock protein 47-collagen 1 chaperone	ND-L02-s0201 (Nitto Denko Corporation)	JUNIPER	2	NCT03538301
Phosphodiesterase 4 (PDE4)	BI 1015550 (Boehringer Ingelheim)		2	NCT04419506
Angiotensin II type 2 (AT_2) receptor	C21 (Vicore Pharma AB)		2	NCT04533022
C-Jun N-terminal kinase	CC-90001 (Celgene)		2	NCT03142191
Estrogen receptor antagonist/telomere maintenance	Danazol		2	NCT03312400
αVβ6 and αVβ1 integrins	PLN-74809 (Pliant Therapeutics)	IPF-201	2a	NCT04396756
			2a	NCT04072315

LPA, lysophosphatidic acid.
[a] Recently completed studies, awaiting results.

inhibitor, is the first approved drug with antifibrotic properties mediated through the inhibition of receptor-mediated downstream signaling of profibrotic mediators such as platelet-derived growth factor, vascular endothelial growth factor, and fibroblast growth factor involved in migration, proliferation, and maturation of fibroblasts and subsequent deposition of ECM [41].

Connective tissue growth factor (CTGF), also known as CCN2, is a small secreted matricellular protein of the CCN family of ECM-associated heparin-binding proteins [42]. As a nonstructural component of the ECM, CTGF binds to various cell surface receptors, including integrin receptors and cell surface heparan sulfate proteoglycans, thus controlling cell signaling, cell–matrix recognition, and cell adhesion. It also binds growth factors such as bone morphogenetic protein 4, TGF-β, and vascular endothelial growth factor, thereby regulating their functions and ECM proteins [42]. There is strong in vitro and ex vivo evidence that TGF-β is a particularly important regulator of CTGF expression. CTGF may account for many of the profibrogenic activities attributed to TGF-β and has been early on identified as a potentially more suitable target for antifibrotic therapies [43]. CTGF levels are elevated in bronchoalveolar lavage of patients with IPF [44], and results from the phase 2 study PRAISE (NCT01890265) with pamrevlumab (FG-3019), a human anti-CTGF monoclonal antibody, showed a significant effect on lung function decline in 160 patients with IPF [45]. Pamrevlumab will be further tested in a phase 3 study ZEPHYRUS (NCT03955146 currently recruiting eligible subjects who are not currently treated with approved therapies for IPF) [46].

The autotaxin–lysophosphatidic acid (LPA) axis is linking pulmonary fibrosis to lung injury by mediating fibroblast recruitment and vascular leak [47]. Autotaxin is a secreted glycoprotein that belongs to the ectonucleotide pyrophosphatase-phosphodiesterase protein family (ENPP) and catalyzes the hydrolysis of lysophosphatidylcholine (lysolecithin) to LPA. LPA-mediated signaling through the LPA1 receptor is involved in multiple cellular processes and pathological conditions including wound healing and fibrosis, through its chemoattracting properties on fibroblasts, binding of integrin $\alpha_v\beta_6$ and TGF-β activation, and endothelial permeabilization [48]. Both autotaxin and LPA levels are elevated in bronchoalveolar lavage of patients with IPF and pulmonary fibrosis models [47,49]. GLPG1690 is a highly specific inhibitor of autotaxin that reduces the levels of LPA and demonstrated antifibrotic properties in preclinical studies and safety and efficacy in the phase 2 trial FLORA (NCT02738801) [50]. Currently, two placebo-controlled phase 3 trials (ISABELA1 and ISABELA2 trials) are recruiting patients. The same pathway is targeted by BMS-986278, a potent small-

molecule LPA receptor antagonist that is currently tested in a study measuring the effectiveness, safety, and tolerability of BMS-986278 in participants with lung fibrosis (NCT04308681).

Galectin-3 is a is a carbohydrate-binding protein that is secreted on infection, damage, and stress by a variety of immune cells, mainly macrophages and other cell types including epithelial cells and fibroblasts [51,52]. Its major role is regulation of damage responses including secretion of profibrotic cytokines such as TNF-α, interleukin (IL) 1β, IL-6, and TGF-β. The role of Gal-3 as a mediator of lung fibrosis has long been studied since the discovery that its levels are elevated in alveolar macrophages after lung injury [53]. In addition, Gal-3 upregulates TGF-β receptors on fibroblasts, leading to elevated collagen I production and fibrotic scar formation, while mice with a genetic deletion of galectin-3 (galectin-3−/−) exhibit less fibrosis in TGF-β1 and bleomycin murine models [52]. Targeting galectin-3 with a small-molecule inhibitor, TD-139, reduced fibrosis in the bleomycin mouse model [52], and effectively reduced Gal-3 expression in bronchoalveolar macrophages are currently being investigated in a phase 2a randamized controlled trial (RCT) [54] and a phase 2b trial (ClinicalTrial.gov identifier: NCT03832946).

Beyond fibroblasts, targeting macrophages, and fibrocytes

The role of immune cells such as macrophages, monocytes, and fibrocytes in the progression of fibrotic lung disease is subject to intense investigation, while pirfenidone and nintedanib as well as an array of novel therapeutic options in IPF effectively alter the activation of these cells [55]. Two molecules that affect directly monocytes and macrophages with promising phase 2 trials are described in the following paragraphs.

Pentraxin 2 or serum amyloid P component (SAP) is predominantly secreted by hepatocytes and inhibits neutrophil recruitment and monocyte-to-fibrocyte differentiation, whereas it promotes phagocytosis by bacteria opsonization and regulates macrophage differentiation toward immunoregulatory and M1 phagocytic macrophages [56]. Compared with controls, patients with renal fibrosis, pulmonary fibrosis, scleroderma, myelofibrosis, rheumatoid arthritis, and mixed connective tissue disease tend to have low levels of SAP, supporting the idea that fibrosis might in part involve a SAP deficiency [56]. In patients with IPF in particular, SAP plasma levels were significantly lower than in healthy controls and positively correlated with FVC, suggesting an association with the severity of lung disease [27]. Preclinical studies with the pulmonary fibrosis murine and rat models of bleomycin intratracheal instillation and lung-driven TGF-β expression demonstrated that SAP injections significantly reduced lung fibrosis through an inhibition of pulmonary fibrocyte and profibrotic alternative (M2) macrophage accumulation [27,57,58]. Injections of recombinant human SAP/PTX2 or PRM-151 improved lung function in a phase 2 trial in patients with pulmonary fibrosis [59], which has led to the initiation of two phase 3 trials (NCT04552899 and NCT04594707).

G protein—coupled receptors 40 and 84 bind free fatty acids and regulate metabolic and inflammatory pathways. GRP84 is highly induced upon inflammatory stimuli in immune cells as well as human fibroblasts and myofibroblasts and is a proinflammatory mediator. The two receptors were recently identified in a new antifibrotic pathway; PBI-4050, 3-pentylbenzeneacetic acid sodium salt, a synthetic analog of a medium-chain fatty acid that displays agonist and antagonist ligand affinity toward the G protein—coupled receptors GPR40 and GPR84, respectively, resulting in the reduction or reversal of fibrosis by regulating macrophages, fibroblasts/myofibroblasts, and epithelial cell responses in several models of fibrosis [60]. Results from a phase 2 study with PBI-4050 (ProMetic BioSciences, Inc.) (NCT02538536) were recently published [61], with encouraging results for PBI-4050 treatment alone or in combination with nintedanib. Results from another GPR84 inhibiting molecule, GLPG1205 (Galápagos NV), are expected from a recently completed phase 2 study (NCT03725852).

Targeted therapies reflecting the patient's genetic and immune condition

Genetic polymorphisms, host immune response abnormalities, and impaired microbe—host interactions leading to shifts in the microbiome in IPF may be a basis for disease endotyping that would guide therapeutic options for patients with IPF.

Shortened telomeres and/or telomere-related mutations are observed in up to one-third of individuals with familial IPF, and 1 in 10 individuals with sporadic IPF have telomere-related mutations. Regardless of Interstitial lung disease (ILD) phenotype, individuals with short telomeres and/or known telomere-related mutations have more rapid disease progression and shorter lung transplant-free survival [15]. Androgens can restore telomerase activity in circulating leukocytes and hematopoietic stem cells from subjects with reduced telomerase function associated with TERT mutations [46,47], on the basis of sex steroid responsiveness of the TERT promoter [62]. A phase 2 trial is currently conducted with the synthetic androgen danazol (NCT03312400), following the results of an early-phase clinical trial with danazol, in patients with short telomeres [63].

The TOLLIP rs3750920 TT genotype is an example of genetic predisposition of the innate immunity arm of patients with IPF that conferred an advantageous effect of n-acetylcysteine (NAC) treatment as opposed to the rs3750920 CC genotype in the PANTHER-IPF study with the tritherapy of prednisone, azathioprine, and N-acetylcysteine [64]. Although the mechanism for this distinct response is not yet clarified, it was hypothesized that Single nucleotide polymorphisms (SNP)-driven differences in TOLLIP-mediated Toll-like receptors (TLR) signaling could lead to an oxidant-driven disease endotype in which NAC therapy would be particularly beneficial [64]. These findings led to a genotype-stratified prospective clinical trial PRECISIONS (NCT04300920) that will compare the effect of NAC plus standard care (nintedanib or pirfenidone) with matched placebo in patients diagnosed with IPF (who have the TOLLIP rs3750920 TT genotype).

Autoimmune self-reactive immunoglobulins can be found in the majority of patients despite the fact that by definition, patients with IPF do not fulfill the (clinical) criteria for an underlying autoimmune disease [65]. Circulating autoantibodies against type V collagen are detectable in approximately 40% of patients [66]. Autoantibody concentrations against intracellular epithelial self-antigens such as annexin-1 and periplakin correlate with outcome measures in IPF, including the development of acute exacerbations [67,68]. Levels of IL-1α autoantibodies were also elevated in the sera of patients with rapidly progressing IPF [69]. Patients with IPF with increased circulating total IgA levels at baseline have a worse prognosis [70]. Abnormal intrapulmonary B-cell aggregates were found in the pulmonary parenchyma together with elevated plasma concentrations of BAFF-R [71]. On the basis of the aforementioned observations, VAY736 (ianalumab), a B-cell depleting, B-cell activating factor receptor blocking, monoclonal antibody will be tested in a phase 2 study (NCT03287414).

Increased microbiome burden has been consistently associated with worse prognosis in IPF, while abundance of streptococcal and staphylococcal bacteria has been associated with an increased risk of disease progression in patients with IPF [30,72,73]. The cause of the increased bacterial burden in the lungs of patients with IPF and its effect on IPF pathogenesis are far from understood, and hypotheses on the genetic background of patients relative to innate and adaptive immunity–related polymorphisms such as TOLLIP and MUC5b and immune senescence are being debated [32,74,75]. Intriguingly, the bacterial burden was lower in patients with IPF with MUC5b rs35705950 T allele [30]. Broad-spectrum antibodies however, such as cotrimoxazole and doxycycline, have provided some encouraging evidence of improved clinical outcomes in IPF and have led to a phase 3 trial CleanUp-IPF, which was however terminated for futility after review of first planned interim analysis.

Improving mitochondrial health and cellular metabolism

Cellular senescence is a common characteristic of the lungs of patients with IPF [76]. Fibroblast senescence and transition to α-SMA–expressing myofibroblasts is part of the natural wound healing process and required for efficient wound closure. It is followed by clearance of senescent cells by monocytes, macrophages, neutrophils, and NK cells. In patients with IPF, however, myofibroblasts/senescent fibroblasts with excessive ECM deposition persist and form the characteristic structure of 'fibroblast foci.' Fibroblast senescence during wound healing should not be confused with cellular senescence caused by aging. Cellular senescence is dependent on factors such as telomere shortening and oxidative stress–induced damage, which in turn is largely related to mitochondrial dysfunction, due to a variety of factors including defective clearance and turnover, accumulation of mitochondrial mutations, and increased mitochondrial oxidation [77,78]. Mitochondrial dysfunction has been recognized as a contributor to fibrosis, and most cell types in lungs of patients with IPF, as in patients with other age-associated chronic diseases, display characteristics of cellular senescence, including fibroblasts, epithelial cells, and cells of the innate and adaptive immune system, such as macrophages [79–81].

Therefore, next to the therapeutic options targeting fibroblast activity, summarized previously, another more global approach in the treatment of IPF is the reversal of cellular senescence by improvement of mitochondrial health, inhibition of telomere attrition, or the elimination of senescent cells by senolytic drugs [82]. GKT137831, an inhibitor of nicotinamide adenine dinucleotide phosphate oxidase isoforms that participate in ROS production, is currently tested in a phase 2 trial (NCT03865927). In addition, selective ablation of senescent cells using dasatinib plus quercetin alleviated IPF-related dysfunction in bleomycin-administered mice, and promising safety results from a phase 1 trial (NCT02874989) were recently reported [83]. Importantly, many options with promising preclinical results which affect mitochondrial health such as thyroid hormone treatment directly improve mitochondrial homeostasis gene expression [84].

Stem cells (e.g. mesenchymal stromal stem cells, induced pluripotent stem cells, and lung stem cells) have also been proposed as a potential therapy for IPF owing to their multipotency and role in tissue repair and wound healing, following promising preclinical data [85–87]. The safety and tolerability of stem cell

administration has been evaluated in phase 1 trials as reviewed in the study by Tzouvelekis et al. [88], and more phase 1 trials are currently recruiting subjects.

Understanding the pathology of IPF from different but interrelated 'optics,' namely, the exposome, genetic predisposition, and dysfunctional metabolic pathways, could be crucial for a holistic disease description. Many metabolic pathways are implicated in the pathogenesis of IPF. The altered metabolism of carbohydrates, lipids, proteins, and hormone modulators has been documented in lung, liver, and kidney fibrosis [89]. Understanding the role of bioactive food ingredients in development of pulmonary fibrosis and adjusting metabolic alterations, reviewed in the studies by Bargagli et al [89] and Mercader-Barceló et al [90], is becoming a new option for antifibrotic therapies. High-fat diet, particularly in saturated fatty acids (SFAs), is associated with increased neutrophil lung infiltration and pulmonary fibrosis [91], while intake of oxidized Low-density lipoprotein (LDL) in silica-induced fibrosis models demonstrated exacerbation of fibrosis owing to the inhibition of the fatty acid scavenger receptor CD36 on alveolar macrophages and the increase in foamy cell formation [92]. The risk of dietary fat and meat consumption in the development of fibrosis was tested in a recent study, which demonstrated that intake of SFAs, monounsaturated fatty acids, n-6 polyunsaturated fatty acids (PUFAs), and meat was independently associated with an increased risk of IPF [93]. Conversely, a diet high in PUFAs in mouse models reduced pulmonary fibrosis, indicating that an adequate dietary PUFA intake might reduce the risk of lung fibrosis development. A higher intake of SFAsrelative to monounsaturated fatty acids was associated with higher incidence of gastrointestinal toxicity related to pirfenidone in the MADIET phase 4 study, suggesting that a significant new approach to be considered in the care of patients with IPF is in the complementation of standard-of-care antifibrotics with dietary habits.

Advanced research, precision medicine, and patient-centeredness

It is crucial to learn how to translate and 'puzzle' evidence to improve IPF management in daily practice. A major issue with IPF is that diagnosis is often late, with loss of lung volume reserve and gas-exchange capacity impairment, already leading to clinical symptoms at the moment of diagnosis. To improve IPF care, emphasis must be given on early diagnosis, risk factor modification, and the identification of phenotypes, most likely to advantage from specific therapeutic interventions [94].

Although some comorbid conditions share risk factors with IPF, the likelihood for their manifestation in patients with IPF is still greater than expected [95]. Some pathogenetic or metabolic effects may share common pathways in experimental models. Furthermore, the in vivo complexity is likely to further influence overall effects or phenotypes. Optimal management of IPF therefore requires a comprehensive approach, which includes management of comorbidities to optimize patient outcomes [95].

For the aforementioned reasons, it is important to revisit the term of patient-centeredness. Patient-centered care was initially introduced in its humanistic meaning by Balint [96] in 1969, and since then, the concept and term have been multilaterally revisited. In 2000, Mead and Bower [97] proposed a conceptual framework to limit the uncertainty of the exact meaning of the term. This led to a biopsychosocial direction by understanding the patient as a person, with shared power and responsibility by his/her doctor, by building therapeutic alliances with and by approaching doctor with his/her human nature as well [97]. Stewart et al. [98], in a primary care study, reported that patient-centered practice improved health status and care quality by 'normalizing' utilization of diagnostic tests and referrals. From relevant research, it is shown that a 'nuclear' behavioral determinant is "knowledge", although this is not abundant element to empower. "Goal setting" and "action planning" were more likely to be promising in obtaining successful interventions [99]. "Knowledge" could be combined with "goal setting" and "action planning" to enhance capacity. To foster effectiveness, a consensus definition for patient empowerment and clinimetric properties of instruments are needed to be studied in conjunction [99].

A major effort is required to ensure that patient-centeredness is the cornerstone to promote high-quality care to seriously ill patients [100], developing methodology (instruments) that monitors patient and family experiences of serious illness care across the patient environment and care delivery sources. Refinements should be settled, based on advanced qualitative techniques with patients, families, and providers in each stage of care, from case registration through ongoing care, care during urgent episodes, and the end-stage moments [100].

Systems biology is a novel research strategy to approach system complexity, and its overall functional epiphenomenon that is often overlooked when one element of system disease pathogenesis is 'decodified' in separation [101]. By launching global initiatives to improve IPF outcomes and by 'smartly' integrating cutting-edge international research that enables systems biology to nurture a precision medicine approach, empowering doctors and patients appears to be decisive steps to undertake toward translational and 'stochastic' care [101]. In Greek, the sociological use of stochastic term refers to wise and aimful thinking. Translating the aforementioned concept in terms of care, offering single

excellence service delivery in isolation may be less effective than multiple good service delivery through integrated care teams and holistic approach.

Extensive research is required before a comprehensive disease fingerprint of IPF can be delivered and before matching this fingerprint to each patient [102]. The adoption of rapidly evolving molecular biology and genomic technologies combined with appropriate bioinformatics data processing and integration of real-time personalized clinical information from patients' micro–macro settings can offer a further opportunity to improve IPF care in terms of outcomes and life quality [102].

In conclusion, bridging disciplines from primary to tertiary care service provision, enhancing patient-centeredness, clinical precision, optimization of service delivery, bioinformatics monitoring, and, of course, biogenomic and metabolic research output by early condensing these ingredients within pregraduate and postgraduate curricula refinements are requisites to support, through operative translational data processing, guidelines, and 'midlines' for effective IPF care in the future.

Credit author statement

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Conflict of interest statement

None declared.

References

Papers of particular interest, published within the period of review, have been highlighted as:

* of special interest
** of outstanding interest

1. Hutchinson J, Fogarty A, Hubbard R, McKeever T: **Global incidence and mortality of idiopathic pulmonary fibrosis: a systematic review**. *Eur Respir J* 2015, **46**:795–806.

2. Karakatsani A, Papakosta D, Rapti A, Antoniou KM, Dimadi M, Markopoulou A, Latsi P, Polychronopoulos V, Birba G, L Ch, *et al.*: **Epidemiology of interstitial lung diseases in Greece**. *Respir Med* 2009, **103**:1122–1129.

3. Olson AL, Gifford AH, Inase N, Fernández Pérez ER, Suda T: **The epidemiology of idiopathic pulmonary fibrosis and interstitial lung diseases at risk of a progressive-fibrosing phenotype**. *Eur Respir Rev* 2018, **27**:180077.

4. Marshall DC, Salciccioli JD, Shea BS, Akuthota P: **Trends in mortality from idiopathic pulmonary fibrosis in the European Union: an observational study of the WHO mortality database from 2001-2013**. *Eur Respir J* 2018:51.

5. Yanagihara T, Sato S, Upagupta C, Kolb M: **What have we learned from basic science studies on idiopathic pulmonary fibrosis?** *Eur Respir Rev* 2019, **28**.

6. ** Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, Behr J, Cottin V, Danoff SK, Morell F, *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.
The latest authoritative clinical practice guidelines for diagnosis of IPF. The newest are under development and expected to be published in 2021.

7. Walsh SLF, Maher TM, Kolb M, Poletti V, Nusser R, Richeldi L, Vancheri C, Wilsher ML, Antoniou KM, Behr J, *et al.*: **Diagnostic accuracy of a clinical diagnosis of idiopathic pulmonary fibrosis: an international case-cohort study**. *Eur Respir J* 2017, **50**.

8. Raghu G, Rochwerg B, Zhang Y, Garcia CA, Azuma A, Behr J, Brozek JL, Collard HR, Cunningham W, Homma S, *et al.*: **An official ATS/ERS/JRS/ALAT clinical practice guideline: treatment of idiopathic pulmonary fibrosis. An update of the 2011 clinical practice guideline**. *Am J Respir Crit Care Med* 2015, **192**:e3–e19.

9. * Lancaster L, Crestani B, Hernandez P, Inoue Y, Wachtlin D, Loaiza L, Quaresma M, Stowasser S, Richeldi L: **Safety and survival data in patients with idiopathic pulmonary fibrosis treated with nintedanib: pooled data from six clinical trials**. *BMJ Open Respiratory Research* 2019, **6**, e000397.
A meta analysis of clinical trials with Nintedanib, that demonstrated a five year increase in the surviva of IPF patients

10. Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, Cottin V, Flaherty KR, Hansell DM, Inoue Y, *et al.*: **Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis**. *N Engl J Med* 2014, **370**:2071–2082.

11. Trachalaki A, Irfan M, Wells AU: **Pharmacological management of Idiopathic Pulmonary Fibrosis: current and emerging options**. *Expet Opin Pharmacother* 2020:1–14.

12. Lederer DJ, Martinez FJ: **Idiopathic pulmonary fibrosis**. *N Engl J Med* 2018, **378**:1811–1823.

13. Wuyts WA, Agostini C, Antoniou KM, Bouros D, Chambers RC, Cottin V, Egan JJ, Lambrecht BN, Lories R, Parfrey H, *et al.*: **The pathogenesis of pulmonary fibrosis: a moving target**. *Eur Respir J* 2013, **41**:1207–1218.

14. Adams TS, Schupp JC, Poli S, Ayaub EA, Neumark N, Ahangari F, Chu SG, Raby BA, Deluliis G, Januszyk M, *et al.*: **Single-cell RNA-seq reveals ectopic and aberrant lung-resident cell populations in idiopathic pulmonary fibrosis**. *Sci Adv* 2020, **6**, eaba1983.

15. Courtwright AM, El-Chemaly S: **Telomeres in interstitial lung disease: the short and the long of it**. *Ann Am Thorac Soc* 2019, **16**:175–181.

16. Mulugeta S, Nureki S, Beers MF: **Lost after translation: insights from pulmonary surfactant for understanding the role of alveolar epithelial dysfunction and cellular quality control in fibrotic lung disease**. *Am J Physiol Lung Cell Mol Physiol* 2015, **309**:L507–L525.

17. Jiang D, Cui H, Xie N, Banerjee S, Liu RM, Dai H, Thannickal VJ, Liu G: **ATF4 mediates mitochondrial unfolded protein response in alveolar epithelial cells**. *Am J Respir Cell Mol Biol* 2020, **63**:478–489.

18. Mora AL, Bueno M, Rojas M: **Mitochondria in the spotlight of aging and idiopathic pulmonary fibrosis**. *J Clin Invest* 2017, **127**:405–414.

19. Katzen J, Beers MF: **Contributions of alveolar epithelial cell quality control to pulmonary fibrosis**. *J Clin Invest* 2020, **130**:5088–5099.

20. Waters DW, Blokland KEC, Pathinayake PS, Burgess JK, Mutsaers SE, Prele CM, Schuliga M, Grainge CL, Knight DA: **Fibroblast senescence in the pathology of idiopathic pulmonary fibrosis**. *Am J Physiol Lung Cell Mol Physiol* 2018, **315**:L162–L172.

21. Heukels P, Moor CC, von der Thüsen JH, Wijsenbeek MS, Kool M: **Inflammation and immunity in IPF pathogenesis and treatment**. *Respir Med* 2019, **147**:79–91.

22. Misharin AV, Morales-Nebreda L, Reyfman PA, Cuda CM, Walter JM, McQuattie-Pimentel AC, Chen CI, Anekalla KR, Joshi N, Williams KJN, *et al.*: **Monocyte-derived alveolar macrophages drive lung fibrosis and persist in the lung over the life span**. *J Exp Med* 2017, **214**:2387–2404.

23. Zhang L, Wang Y, Wu G, Xiong W, Gu W, Wang CY: **Macrophages: friend or foe in idiopathic pulmonary fibrosis?** *Respir Res* 2018, **19**:170.

24. Reilkoff RA, Bucala R, Herzog EL: **Fibrocytes: emerging effector cells in chronic inflammation**. *Nat Rev Immunol* 2011, **11**:427–435.

25. Reyfman PA, Walter JM, Joshi N, Anekalla KR, McQuattie-Pimentel AC, Chiu S, Fernandez R, Akbarpour M, Chen CI, Ren Z, *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.

26. van de Garde MD, Martinez FO, Melgert BN, Hylkema MN, Jonkers RE, Hamann J: **Chronic exposure to glucocorticoids shapes gene expression and modulates innate and adaptive activation pathways in macrophages with distinct changes in leukocyte attraction**. *J Immunol* 2014, **192**:1196–1208.

27. Murray LA, Chen Q, Kramer MS, Hesson DP, Argentieri RL, Peng X, Gulati M, Homer RJ, Russell T, van Rooijen N, *et al.*: **TGF-beta driven lung fibrosis is macrophage dependent and blocked by Serum amyloid P**. *Int J Biochem Cell Biol* 2011, **43**:154–162.

28. Seibold MA, Wise AL, Speer MC, Steele MP, Brown KK, Loyd JE, Fingerlin TE, Zhang W, Gudmundsson G, Groshong SD, *et al.*: **A common MUC5B promoter polymorphism and pulmonary fibrosis**. *N Engl J Med* 2011, **364**:1503–1512.

29. Noth I, Zhang Y, Ma SF, Flores C, Barber M, Huang Y, Broderick SM, Wade MS, Hysi P, Scuirba J, *et al.*: **Genetic variants associated with idiopathic pulmonary fibrosis susceptibility and mortality: a genome-wide association study**. *Lancet Respir Med* 2013, **1**:309–317.

30. Molyneaux PL, Cox MJ, Willis-Owen SA, Mallia P, Russell KE, Russell AM, Murphy E, Johnston SL, Schwartz DA, Wells AU, *et al.*: **The role of bacteria in the pathogenesis and progression of idiopathic pulmonary fibrosis**. *Am J Respir Crit Care Med* 2014, **190**:906–913.

31. D'Alessandro-Gabazza CN, Kobayashi T, Yasuma T, Toda M, Kim H, Fujimoto H, Hataji O, Takeshita A, Nishihama K, Okano T, *et al.*: **A Staphylococcus pro-apoptotic peptide induces acute exacerbation of pulmonary fibrosis**. *Nat Commun* 2020, **11**:1539.

32. Lipinski JH, Moore BB, O'Dwyer DN: **The evolving role of the lung microbiome in pulmonary fibrosis**. *Am J Physiol Lung Cell Mol Physiol* 2020, **319**:L675–L682.

33. Brownell R, Kaminski N, Woodruff PG, Bradford WZ, Richeldi L, Martinez FJ, Collard HR: **Precision medicine: the new frontier in idiopathic pulmonary fibrosis**. *Am J Respir Crit Care Med* 2016, **193**:1213–1218.

34. Spagnolo P, Bonella F, Ryerson CJ, Tzouvelekis A, Maher TM: **Shedding light on developmental drugs for idiopathic pulmonary fibrosis**. *Expet Opin Invest Drugs* 2020, **29**:797–808.

35. Saito S, Alkhatib A, Kolls JK, Kondoh Y, Lasky JA: **Pharmacotherapy and adjunctive treatment for idiopathic pulmonary fibrosis (IPF)**. *J Thorac Dis* 2019, **11**:S1740–S1754.

36. Sgalla G, Iovene B, Calvello M, Ori M, Varone F, Richeldi L: **Idiopathic pulmonary fibrosis: pathogenesis and management**. *Respir Res* 2018, **19**:32.

37. Richeldi L, Baldi F, Pasciuto G, Macagno F, Panico L: **Current and future idiopathic pulmonary fibrosis therapy**. *Am J Med Sci* 2019, **357**:370–373.

38. Somogyi V, Chaudhuri N, Torrisi SE, Kahn N, Müller V, Kreuter M: **The therapy of idiopathic pulmonary fibrosis: what is next?** *Eur Respir Rev* 2019, **28**.

39. Hewitt RJ, Maher TM: **Idiopathic pulmonary fibrosis: new and emerging treatment options**. *Drugs Aging* 2019, **36**:485–492.

40. Sgalla G, Flore M, Siciliano M, Richeldi L: **Antibody-based therapies for idiopathic pulmonary fibrosis**. *Expet Opin Biol Ther* 2020, **20**:779–786.

41. Wollin L, Wex E, Pautsch A, Schnapp G, Hostettler KE, Stowasser S, Kolb M: **Mode of action of nintedanib in the treatment of idiopathic pulmonary fibrosis**. *Eur Respir J* 2015, **45**:1434–1445. ERJ-01749-02014.

42. Ponticos M: **Connective tissue growth factor (CCN2) in blood vessels**. *Vasc Pharmacol* 2013, **58**:189–193.

43. Allen JT, Spiteri MA: **Growth factors in idiopathic pulmonary fibrosis: relative roles**. *Respir Res* 2002, **3**:13.

44. Yang J, Velikoff M, Canalis E, Horowitz JC, Kim KK: **Activated alveolar epithelial cells initiate fibrosis through autocrine and paracrine secretion of connective tissue growth factor**. *Am J Physiol Lung Cell Mol Physiol* 2014, **306**:L786–L796.

45. ** Richeldi L, Fernández Pérez ER, Costabel U, Albera C, Lederer DJ, Flaherty KR, Ettinger N, Perez R, Scholand MB, Goldin J, *et al.*: **Pamrevlumab, an anti-connective tissue growth factor therapy, for idiopathic pulmonary fibrosis (PRAISE): a phase 2, randomised, double-blind, placebo-controlled trial**. *Lancet Respir Med* 2020, **8**:25–33.

Results from the phase 2 study PRAISE with pamrevlumab (FG-3019), a human anti-CTGF monoclonal antibody showed a significant effect on lung function decline of 160 IPF patients.

46. Sgalla G, Franciosa C, Simonetti J, Richeldi L: **Pamrevlumab for the treatment of idiopathic pulmonary fibrosis**. *Expet Opin Invest Drugs* 2020, **29**:771–777.

47. Tager AM, LaCamera P, Shea BS, Campanella GS, Selman M, Zhao Z, Polosukhin V, Wain J, Karimi-Shah BA, Kim ND, *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.

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

49. Oikonomou N, Mouratis MA, Tzouvelekis A, Kaffe E, Valavanis C, Vilaras G, Karameris A, Prestwich GD, Bouros D, Aidinis V: **Pulmonary autotaxin expression contributes to the pathogenesis of pulmonary fibrosis**. *Am J Respir Cell Mol Biol* 2012, **47**:566–574.

50. ** Maher TM, van der Aar EM, Van de Steen O, Allamassey L, Desrivot J, Dupont S, Fagard L, Ford P, Fieuw A, Wuyts W: **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.

Results from the phase 2 trial FLORA with GLPG1690 a specific inhibitor of autotaxin demonstrating anti-fibrotic properties, safety and efficacy.

51. Henderson NC, Mackinnon AC, Farnworth SL, Poirier F, Russo FP, Iredale JP, Haslett C, Simpson KJ, Sethi T: **Galectin-3 regulates myofibroblast activation and hepatic fibrosis**. *Proc Natl Acad Sci U S A* 2006, **103**:5060–5065.

52. Henderson NC, Mackinnon AC, Farnworth SL, Kipari T, Haslett C, Iredale JP, Liu FT, Hughes J, Sethi T: **Galectin-3 expression and secretion links macrophages to the promotion of renal fibrosis**. *Am J Pathol* 2008, **172**:288–298.

53. Ho JE, Gao W, Levy D, Santhanakrishnan R, Araki T, Rosas IO, Hatabu H, Latourelle JC, Nishino M, Dupuis J, *et al.*: **Galectin-3 is associated with restrictive lung disease and interstitial lung abnormalities**. *Am J Respir Crit Care Med* 2016, **194**:77–83.

54. Hirani N, Nicol L, MacKinnon AC, Ford P, Schambye H, Pedersen, Nilsson U, Leffler H, Thomas T, Knott O, *et al.*: **TD139, A novel inhaled galectin-3 inhibitor for the treatment of idiopathic pulmonary fibrosis (IPF). Results from the first in (IPF) patients study**. *QJM: Int J Med* 2016, **109**:S16. S16.

55. Liu G, Zhai H, Zhang T, Li S, Li N, Chen J, Gu M, Qin Z, Liu X: **New therapeutic strategies for IPF: based on the**

"phagocytosis-secretion-immunization" network regulation mechanism of pulmonary macrophages. *Biomed Pharmacother* 2019, **118**:109230.

56. Pilling D, Gomer RH: **The development of serum amyloid P as a possible therapeutic**. *Front Immunol* 2018, **9**:2328.

57. Murray LA, Rosada R, Moreira AP, Joshi A, Kramer MS, Hesson DP, Argentieri RL, Mathai S, Gulati M, Herzog EL, *et al.*: **Serum amyloid P therapeutically attenuates murine bleomycin-induced pulmonary fibrosis via its effects on macrophages**. *PloS One* 2010, **5**, e9683.

58. Pilling D, Roife D, Wang M, Ronkainen SD, Crawford JR, Travis EL, Gomer RH: **Reduction of bleomycin-induced pulmonary fibrosis by serum amyloid P**. *J Immunol* 2007, **179**: 4035–4044.

59. * Raghu G, van den Blink B, Hamblin MJ, Brown AW, Golden JA, Ho LA, Wijsenbeek MS, Vasakova M, Pesci A, Antin-Ozerkis DE, *et al.*: **Effect of recombinant human pentraxin 2 vs placebo on change in forced vital capacity in patients with idiopathic pulmonary fibrosis: a randomized clinical trial**. *Jama* 2018, **319**:2299–2307.

A phase 2 trial with injections of recombinant human SAP/PTX2 or PRM-151 showing improved lung function in pulmonary fibrosis patients

60. Gagnon L, Leduc M, Thibodeau JF, Zhang MZ, Grouix B, Sarra-Bournet F, Gagnon W, Hince K, Tremblay M, Geerts L, *et al.*: **A newly discovered antifibrotic pathway regulated by two fatty acid receptors: GPR40 and GPR84**. *Am J Pathol* 2018, **188**:1132–1148.

61. * Khalil N, Manganas H, Ryerson CJ, Shapera S, Cantin AM, Hernandez P, Turcotte EE, Parker JM, Moran JE, Albert GR, *et al.*: **Phase 2 clinical trial of PBI-4050 in patients with idiopathic pulmonary fibrosis**. *Eur Respir J* 2019, **53**.

Results from a phase 2 study with PBI-4050 with encouraging results for PBI-4050 treatment alone or in combination with Nintedanib.

62. Chambers DC, Lutzky VP, Apte SH, Godbolt D, Feenstra J, Mackintosh J: **Successful treatment of telomeropathy-related interstitial lung disease with immunosuppression and danazol**. *Respirol Case Rep* 2020, **8**, e00607.

63. Townsley DM, Dumitriu B, Liu D, Biancotto A, Weinstein B, Chen C, Hardy N, Mihalek AD, Lingala S, Kim YJ, *et al.*: **Danazol treatment for telomere diseases**. *N Engl J Med* 2016, **374**: 1922–1931.

64. Oldham JM, Ma SF, Martinez FJ, Anstrom KJ, Raghu G, Schwartz DA, Valenzi E, Witt L, Lee C, Vij R, *et al.*: **TOLLIP, MUC5B, and the response to N-acetylcysteine among individuals with idiopathic pulmonary fibrosis**. *Am J Respir Crit Care Med* 2015, **192**:1475–1482.

65. Magro CM, Waldman WJ, Knight DA, Allen JN, Nadasdy T, Frambach GE, Ross P, Marsh CB: **Idiopathic pulmonary fibrosis related to endothelial injury and antiendothelial cell antibodies**. *Hum Immunol* 2006, **67**:284–297.

66. Vittal R, Mickler EA, Fisher AJ, Zhang C, Rothhaar K, Gu H, Brown KM, Emtiazjoo A, Lott JM, Frye SB, *et al.*: **Type V collagen induced tolerance suppresses collagen deposition, TGF-β and associated transcripts in pulmonary fibrosis**. *PloS One* 2013, **8**, e76451.

67. Ogushi F, Tani K, Endo T, Tada H, Kawano T, Asano T, Huang L, Ohmoto Y, Muraguchi M, Moriguchi H, *et al.*: **Autoantibodies to IL-1 alpha in sera from rapidly progressive idiopathic pulmonary fibrosis**. *J Med Invest* 2001, **48**:181–189.

68. Taillé C, Grootenboer-Mignot S, Boursier C, Michel L, Debray MP, Fagart J, Barrientos L, Mailleux A, Cigna N, Tubach F, *et al.*: **Identification of periplakin as a new target for autoreactivity in idiopathic pulmonary fibrosis**. *Am J Respir Crit Care Med* 2011, **183**:759–766.

69. Kurosu K, Takiguchi Y, Okada O, Yumoto N, Sakao S, Tada Y, Kasahara Y, Tanabe N, Tatsumi K, Weiden M, *et al.*: **Identification of annexin 1 as a novel autoantigen in acute exacerbation of idiopathic pulmonary fibrosis**. *J Immunol* 2008, **181**: 756–767.

70. Ten Klooster L, van Moorsel CH, Kwakkel-van Erp JM, van Velzen-Blad H, Grutters JC: **Immunoglobulin A in serum: an old acquaintance as a new prognostic biomarker in idiopathic pulmonary fibrosis**. *Clin Exp Immunol* 2015, **181**:357–361.

71. Xue J, Kass DJ, Bon J, Vuga L, Tan J, Csizmadia E, Otterbein L, Soejima M, Levesque MC, Gibson KF, *et al.*: **Plasma B lymphocyte stimulator and B cell differentiation in idiopathic pulmonary fibrosis patients**. *J Immunol* 2013, **191**:2089–2095.

72. Invernizzi R, Barnett J, Rawal B, Nair A, Ghai P, Kingston S, Chua F, Wu Z, Wells AU, Renzoni ER, *et al.*: **Bacterial burden in the lower airways predicts disease progression in idiopathic pulmonary fibrosis and is independent of radiological disease extent**. *Eur Respir J* 2020, **55**.

73. Han MK, Zhou Y, Murray S, Tayob N, Noth I, Lama VN, Moore BB, White ES, Flaherty KR, Huffnagle GB, *et al.*: **Lung microbiome and disease progression in idiopathic pulmonary fibrosis: an analysis of the COMET study**. *Lancet Respir Med* 2014, **2**:548–556.

74. Dickson RP, Harari S, Kolb M: **Making the case for causality: what role do lung microbiota play in idiopathic pulmonary fibrosis?** *Eur Respir J* 2020:55.

75. Schwartz DA: **Idiopathic pulmonary fibrosis is a genetic disease involving mucus and the peripheral airways**. *Ann Am Thorac Soc* 2018, **15**:S192–S197.

76. Schafer MJ, White TA, Iijima K, Haak AJ, Ligresti G, Atkinson EJ, Oberg AL, Birch J, Salmonowicz H, Zhu Y, *et al.*: **Cellular senescence mediates fibrotic pulmonary disease**. *Nat Commun* 2017, **8**:14532.

77. Birch J, Barnes PJ, Passos JF: **Mitochondria, telomeres and cell senescence: implications for lung ageing and disease**. *Pharmacol Ther* 2018, **183**:34–49.

78. Gorgoulis V, Adams PD, Alimonti A, Bennett DC, Bischof O, Bishop C, Campisi J, Collado M, Evangelou K, Ferbeyre G, *et al.*: **Cellular senescence: defining a path forward**. *Cell* 2019, **179**: 813–827.

79. Álvarez D, Cárdenes N, Sellarés J, Bueno M, Corey C, Hanumanthu VS, Peng Y, D'Cunha H, Sembrat J, Nouraie M, *et al.*: **IPF lung fibroblasts have a senescent phenotype**. *Am J Physiol Lung Cell Mol Physiol* 2017, **313**:L1164–L1173.

80. Tsitoura E, Vasarmidi E, Bibaki E, Trachalaki A, Koutoulaki C, Papastratigakis G, Papadogiorgaki S, Chalepakis G, Tzanakis N, Antoniou KM: **Accumulation of damaged mitochondria in alveolar macrophages with reduced OXPHOS related gene expression in IPF**. *Respir Res* 2019, **20**:264.

81. Bueno M, Lai YC, Romero Y, Brands J, St Croix CM, Kamga C, Corey C, Herazo-Maya JD, Sembrat J, Lee JS, *et al.*: **PINK1 deficiency impairs mitochondrial homeostasis and promotes lung fibrosis**. *J Clin Invest* 2015, **125**:521–538.

82. Lehmann M, Korfei M, Mutze K, Klee S, Skronska-Wasek W, Alsafadi HN, Ota C, Costa R, Schiller HB, Lindner M, *et al.*: **Senolytic drugs target alveolar epithelial cell function and attenuate experimental lung fibrosis ex vivo**. *Eur Respir J* 2017, **50**.

83. Justice JN, Nambiar AM, Tchkonia T, LeBrasseur NK, Pascual R, Hashmi SK, Prata L, Masternak MM, Kritchevsky SB, Musi N, *et al.*: **Senolytics in idiopathic pulmonary fibrosis: results from a first-in-human, open-label, pilot study**. *EBioMedicine* 2019, **40**:554–563.

84. * Yu G, Tzouvelekis A, Wang R, Herazo-Maya JD, Ibarra GH, Srivastava A, de Castro Jpw, DeIuliis G, Ahangari F, Woolard T, *et al.*: **Thyroid hormone inhibits lung fibrosis in mice by improving epithelial mitochondrial function**. *Nat Med* 2018, **24**:39–49.

Thyroid hormone as an option of improvement of mitochondria health in IPF.

85. Antoniou KM, Karagiannis K, Tsitoura E, Bibaki E, Lasithiotaki I, Proklou A, Spandidos DA, Tzanakis N: **Clinical applications of mesenchymal stem cells in chronic lung diseases**. *Biomed Rep* 2018, **8**:314–318.

86. Wecht S, Rojas M: **Mesenchymal stem cells in the treatment of chronic lung disease**. *Respirology* 2016, **21**:1366–1375.

87. Antoniou KM, Karagiannis K, Tsitoura E, Tzanakis N: **Mesenchymal stem cell treatment for IPF-time for phase 2 trials?** *Lancet Respir Med* 2017, **5**:472–473.

88. Tzouvelekis A, Toonkel R, Karampitsakos T, Medapalli K, Ninou I, Aidinis V, Bouros D, Glassberg MK: **Mesenchymal stem cells for the treatment of idiopathic pulmonary fibrosis**. *Front Med* 2018, **5**:142.

89. Bargagli E, Refini RM, d'Alessandro M, Bergantini L, Cameli P, Vantaggiato L, Bini L, Landi C: **Metabolic dysregulation in idiopathic pulmonary fibrosis**. *Int J Mol Sci* 2020:21.

90. Mercader-Barceló J, Truyols-Vives J, Río C, López-Safont N, Sala-Llinàs E, Chaplin A: **Insights into the role of bioactive food ingredients and the microbiome in idiopathic pulmonary fibrosis**. *Int J Mol Sci* 2020:21.

91. Vedova MCD, Soler Garcia FM, Muñoz MD, Fornes MW, Gomez Mejiba SE, Gómez NN, Ramirez DC: **Diet-induced pulmonary inflammation and incipient fibrosis in mice: a possible role of neutrophilic inflammation**. *Inflammation* 2019, **42**:1886–1900.

92. Hou X, Summer R, Chen Z, Tian Y, Ma J, Cui J, Hao X, Guo L, Xu H, Wang H, *et al.*: **Lipid uptake by alveolar macrophages drives fibrotic responses to silica dust**. *Sci Rep* 2019, **9**:399.

93. Miyake Y, Sasaki S, Yokoyama T, Chida K, Azuma A, Suda T, Kudoh S, Sakamoto N, Okamoto K, Kobashi G, *et al.*: **Dietary fat and meat intake and idiopathic pulmonary fibrosis: a case-control study in Japan**. *Int J Tubercul Lung Dis* 2006, **10**: 333–339.

94. Ding Q, Luckhardt T, Hecker L, Zhou Y, Liu G, Antony VB, deAndrade J, Thannickal VJ: **New insights into the pathogenesis and treatment of idiopathic pulmonary fibrosis**. *Drugs* 2011, **71**:981–1001.

95. King CS, Nathan SD: **Idiopathic pulmonary fibrosis: effects and optimal management of comorbidities**. *Lancet Respir Med* 2017, **5**:72–84.

96. Balint E: **The possibilities of patient-centered medicine**. *J Roy Coll Gen Pract* 1969, **17**:269–276.

97. Mead N, Bower P: **Patient-centredness: a conceptual framework and review of the empirical literature**. *Soc Sci Med* 2000, **51**:1087–1110.

98. Stewart M, Brown JB, Donner A, McWhinney IR, Oates J, Weston WW, Jordan J: **The impact of patient-centered care on outcomes**. *J Fam Pract* 2000, **49**:796–804.

99. Werbrouck A, Swinnen E, Kerckhofs E, Buyl R, Beckwée D, De Wit L: **How to empower patients? A systematic review and meta-analysis**. *Transl Behav Med* 2018, **8**:660–674.

100. Anhang Price R, Elliott MN: **Measuring patient-centeredness of care for seriously ill individuals: challenges and opportunities for accountability initiatives**. *J Palliat Med* 2018, **21**:S28–S35.

101. Molina-Molina M, Agusti A, Crestani B, Schwartz DA, Königshoff M, Chambers RC, Maher TM, Faner R, Mora AL, Rojas M, *et al.*: **Towards a global initiative for fibrosis treatment (GIFT)**. *ERJ Open Res* 2017, **3**.

102. Spagnolo P, Cottin V: **Genetics of idiopathic pulmonary fibrosis: from mechanistic pathways to personalised medicine**. *J Med Genet* 2017, **54**:93–99.