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Idiopathic pulmonary fibrosis: disease mechanisms and drug development

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Abstract

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive disease of unknown cause characterized by relentless scarring of the lung parenchyma leading to reduced quality of life and earlier mortality. IPF is an age-related disorder, and with the population aging worldwide, the economic burden of IPF is expected to steadily increase in the future. The mechanisms of fibrosis in IPF remain elusive, with favored concepts of disease pathogenesis involving recurrent microinjuries to a genetically predisposed alveolar epithelium, followed by an aberrant reparative response characterized by excessive collagen deposition. Pirfenidone and nintedanib are approved for treatment of IPF based on their ability to slow functional decline and disease progression; however, they do not offer a cure and are associated with tolerability issues. In this review, we critically discuss how cutting-edge research in disease pathogenesis may translate into identification of new therapeutic targets, thus facilitate drug discovery. There is a growing portfolio of treatment options for IPF. However, targeting the multitude of profibrotic cytokines

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and growth factors involved in disease pathogenesis may require a combination of therapeutic strategies with different mechanisms of action.

Keywords

idiopathic pulmonary fibrosis; pathogenesis; disease mechanisms; genomics; single-cell biology; treatment; therapeutic targets; stem cells

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive age-related interstitial lung disease (ILD) of unknown origin with an average life expectancy of 3–5 years after diagnosis if untreated (Lederer and Martinez, 2018; Raghu et al 2018). In Europe alone, approximately 40,000 new cases of IPF are diagnosed each year (Navaratnam et al 2011). The physical, psychologic, and socio-economic burden of IPF is substantial (Diamantopoulos et al 2018), and with the population aging worldwide, the impact of IPF to patients and healthcare providers is expected to steadily increase in the future. IPF is the prototypic progressive fibrosing ILD, but a number of other ILDs can also display a progressive phenotype and a clinical course similar to IPF (Cottin et al 2018).

Although the mechanisms of fibrosis in IPF remain poorly understood, favored concepts of disease pathogenesis involve recurrent subclinical injuries to a genetically predisposed alveolar epithelium, followed by failure of alveolar re-epithelialization and repair (Spagnolo and Cottin 2017). Activated cells within the alveoli release a plethora of cytokines and growth factors that promote the recruitment, proliferation, and differentiation of lung fibroblasts into myofibroblasts, leading to excessive collagen deposition, progressive scarring of the lung parenchyma, and irreversible loss of function (Bellaye et al 2015; Wolters et al 2014). Current evidence-based guidelines for treatment of IPF recommend the use of pirfenidone and nintedanib, two compounds with pleiotropic mechanisms of action (Raghu et al 2015; Spagnolo et al 2015; Spagnolo et al 2018); however, both drugs have limited efficacy in preventing disease progression and improving quality of life, and are also associated with tolerability issues (Galli et al 2017; Bando et al 2016). Lung transplant is the only cure for patients with IPF, but, due to age and comorbidities, this represents a realistic therapeutic option for only a minority of patients (George et al 2019).

These characteristics of IPF indicate the ongoing critical importance of drug discovery efforts. In this review, we critically discuss how cutting-edge research in disease pathogenesis may translate into identification of new therapeutic targets that are needed to facilitate discovery and testing of new medications that can further slow or ideally stop the progression of IPF.

2. Pathogenesis

Whilst inflammatory cells and the mesenchyme were once the primary focus of IPF research, significant progress over the past two decades has led to the current paradigm of IPF pathogenesis, which proposes that, in a genetically susceptible individual, recurrent

environmental and/or endogenous injury to alveolar epithelium occurs, with increased cell death, aberrant epithelial repair, and dysregulated epithelial-fibroblast cross-talk promoting persistent mesenchymal activation and extracellular matrix (ECM) deposition (Richeldi et al 2017). The importance of dysregulation of alveolar epithelial cells in the initiation of pulmonary fibrosis has been strengthened by the recent observation that an IPF-associated mutation in the surfactant protein C gene, an alveolar type II (AT2) cell-restricted protein, is sufficient in mice to induce spontaneous lung fibrosis, the first model derived from an IPF-associated gene that has been demonstrated to develop spontaneous lung fibrosis (Nureki et al 2018).

The complexity of IPF biology is demonstrated by the number of cell types and signalling pathways that have now been implicated in disease pathogenesis such as dysregulated epithelial repair, host defence, cell senescence, skewed immune responses including activation of macrophage subsets, fibroproliferative responses linked to aberrant kinase activation, transforming growth factor- β (TGF- β) and its downstream pro-fibrogenic pathways, and developmental pathway reactivation (Richeldi et al 2017). The spatial heterogeneity of IPF further complicates pathogenesis studies, as it is plausible that different biological processes reflecting different disease stages are present in one IPF lung in different areas at the same time. The application of single-cell RNA sequencing (scRNA-seq) approaches to IPF tissue has begun to address these challenges, with recent studies identifying diverse aberrant cell populations in IPF tissue which are now the subject of active investigation to dissect mechanisms underlying their dysregulation and potential therapeutic targeting (Habermann et al 2020; Adams et al 2020; Reyfman et al 2019; Xu 2016; Morse et al 2019; Jones et al 2018).

A number of factors that may underlie dysfunction of AT2 cells in IPF have been proposed including telomere shortening, aberrant mitochondrial bioenergetics, and increased endoplasmic reticulum stress. AT2 cells function as distal epithelial stem cells in the adult lung and so have a key role for regeneration and repair of an injured alveolus (Yu et al 2018; Bueno et al 2015; Naikawadi et al 2016; Korfei et al 2008; Lawson et al 2008). Studies have now identified homeostatic determinants of a progenitor cell niche for AT2 cells including Wnt signalling and hyaluronan (Nabhan et al 2018; Zacharias et al 2018; Liang et al 2016). It has recently been reported that during normal tissue regeneration, prior to terminal maturation into alveolar Type 1 cells, AT2 cells acquire a pre-alveolar type 1 transitional cell state during which time they express senescence-related genes (Kobayashi 2020). Accumulation of pre-alveolar type 1 transitional cell state -like cells have been reported in IPF lungs, suggesting that aberrant differentiation or persistence of this transitional cell senescence state might prevent normal alveolar regeneration and so could promote fibrosis development. Notably, a novel mouse model of conditional p53-dependent AT2 senescence has now been shown to develop spontaneous, progressive pulmonary fibrosis (Yao et al 2020).

Dysfunction of alveolar epithelium is proposed to be a key step in IPF disease initiation, although the factors that determine the persistence and progression of fibrosis remain poorly defined, with both cell intrinsic as well as local microenvironmental factors such as the ECM under active investigation. Until recently, ECM deposition was considered simply the end-

stage of fibrosis, but there is now evidence that abnormal ECM deposition itself might modulate disease behaviour, with both altered ECM composition and increased tissue stiffness proposed to dysregulate cell behaviour to induce a positive feedback loop of self-sustaining fibrosis (Booth et al 2012; Parker et al 2014; Morse et al 2019).

IPF has generally been considered an alveolar disease that spares the airways; however, micro computed tomography analyses have now proposed that small airways changes are an early pathologic feature of IPF, identifying thickening of small airway walls together with significant loss of terminal bronchioles within regions of minimal fibrosis (Verleden et al 2020). Consistent with this concept a common gain-of-function *MUC5B* promoter variant (rs35705950), which is the strongest risk factor for the development of IPF, is over-expressed in bronchoalveolar epithelium and it has been hypothesized that excessive production of MUC5B may either enhance injury at the bronchoalveolar junction due to reduced muco-ciliary clearance or impede repair consequent to disruption of normal regenerative mechanisms in the distal lung (Seibold et al 2011; Schwartz, 2018).

Once considered sterile it is now recognised that the epithelial surface of the respiratory tract is colonized by a complex and dynamic microbiota termed the “lung microbiome”. In recent years studies performing culture-independent microbiological analysis of the lung microbiome have suggested that altered lung microbiome burden, diversity and composition in the airways of patients with IPF may contribute to disease pathogenesis and progression (O’Dwyer et al 2019). Whilst causality for the identified associations has yet to be established, murine model studies are supportive of this concept proposing that lung dysbiosis precedes peak lung injury and can promote alveolar inflammation and aberrant repair (O’Dwyer et al 2019; Molyneaux et al 2014; Molyneaux et al 2017; Han 2014).

2.1 The fibroblastic foci

Histopathologically, IPF is defined by the morphologic pattern of usual interstitial pneumonia, which is characterized by spatial heterogeneity, with areas of marked fibrosis adjacent to normal appearing lung, architectural distortion, microscopic honeycombing (cystic spaces lined by bronchiolar epithelium) and scattered *fibroblastic foci* (FF), which are believed to represent sites of active fibrogenesis (Cavazza et al 2010; Katzenstein et al 2008; Wuyts et al 2014; Rossi and Spagnolo 2017). FF are enigmatic aggregates of mesenchymal cells within a myxoid appearing matrix, which in 3D have been identified to be heterogeneous structures with large variations in shape and volume, consistent with the concept that they are temporally distinct microscopic foci of dysregulated lung injury and repair (Jones et al 2016). Whilst the mesenchymal cellular populations within FF remain poorly defined, scRNA-seq studies have provided new insights into aberrant cell populations within and adjacent to FF, identifying that the cuboidal epithelial cells overlying FF are aberrant basaloid cells co-expressing basal epithelial, mesenchymal, senescence, and developmental markers (Adams et al 2020), whilst a pro-fibrotic macrophage sub-population highly expressing secreted phosphoprotein 1 has been localised surrounding and within FF (Morse et al 2019). Although speculative, it is plausible that dysregulated cross-talk between these cell populations could represent a core pathway of progressive lung fibrogenesis.

Several studies have focused on functional characterization of FF (Harada 2010; Myllärniemi 2014; Chilosi 2017). Within FF, alveolar epithelial cells (AECs) and myofibroblasts show disruption of the Wnt/beta-catenin pathway, downregulation of phosphatase and tensin homolog, a multi-functional tumor suppressor, and overexpression of gremlin (an oncoprotein) and TGF- β , leading to epithelial-to-mesenchymal transition (Harada et al 2010; Myllärniemi et al 2014; Chilosi et al 2017). AECs and myofibroblasts also overexpress matrix metalloproteinases as well as a number of profibrotic proteins such as Zinc finger E-box-binding homeobox 1 and beta-tubulin III (Chilosi et al 2017; Hill et al 2019). Within the FF, AECs (but not myofibroblasts; Giulio Rossi, personal unpublished observation; Figure 1) overexpress c-MET, a receptor tyrosine kinase, which binds to its ligand, hepatocyte growth factor, to activate a wide range of signaling pathways involved in cell proliferation, motility, migration and invasion (Organ and Tsao, 2011). Therapeutic inhibition of c-MET may potentially interfere with epithelial-to-mesenchymal transition and FF formation in IPF (Tzouvelekis et al 2019).

3. Establishing a plausible rationale for novel targets

Identifying novel targets for therapy in IPF requires a clear understanding of disease pathogenesis, genetic risk factors, and biomarkers of disease progression. With this foundation, application of traditional and novel drug discovery approaches can be performed to identify therapeutic targets for this progressive disease. The traditional approach to drug discovery is hypothesis-driven with testing of molecular targets first in *in vitro* and *in vivo* systems, including animal models. Promising targets are then transitioned into the clinical trial phases in order to demonstrate safety and efficacy (Mahan, 2014). Phase I studies are used to test safety in humans and may also be used to evaluate the best way to administer a drug, including its frequency, dose, and occasionally route of administration. Phase II studies subsequently involve testing people with the disease, to assess either efficacy or safety or both. Finally, more definitive Phase III studies are typically conducted in many centers across several countries with a large enough sample size to detect a meaningful benefit in whatever endpoint provides the optimal balance between clinical relevance and feasibility. Once a target has gone through all of these phases, data are presented to the relevant regulatory authorities to assess effectiveness and to ensure safety and manufacturing quality standards will be met. Only then is a marketing authorization or license issued. Unfortunately, this traditional method is a long and demanding process, with many candidate targets never making it to clinical trials (Moore, 2003). Even those candidates that make it to the trial phases are hampered by cost, recruitment issues, and time.

In recent years, there has been a push for novel methods to identify candidate targets to accelerate drug discovery. High throughput assays, for example, have been proposed in this context (Hughes et al 2011). These assays leverage technology to screen a large number of biological modulators and effectors against specific targets in relevant biological systems. Some novel biological systems being investigated in IPF include organoids (Wilkinson et al 2017) and scar-in-a-jar (Chen et al 2009), among others. Another approach that is gaining traction includes drug repurposing. This strategy consists of using existing drugs and identifying new uses outside the original indications. Attempted examples of this strategy in IPF include metformin (Kheirollahi et al 2019; Rangarajan 2018), and Phosphoinositide 3-

kinase / mammalian target of rapamycin inhibitor (Mercer et al 2016; Lukey et al 2019; Woodcock et al 2019). Leveraging off-target effects provides a more cost effective and more efficient way to identify new drugs given that they have already gone through rigorous safety assessments. Last, smarter clinical trial design is being explored (Sessler and Myles, 2020).

Strategies for traditional randomized trials include enriching trial populations for those more likely to progress, using biomarkers to determine who may be more likely to respond to an intervention, or using novel endpoints. Limitations to this approach remain cost, recruitment delays, rigidity of the study protocol, and potentially decreased generalizability outside of the narrow clinical trial population. Other novel trial designs that may avoid some of these limitations without sacrificing validity or study integrity include adaptive, pragmatic, cluster crossover, and stepped wedge trial designs (Sessler and Myles, 2020). For example, adaptive designs use interim data to modify an ongoing trial without compromising validity or introducing bias. There are benefits of this design for rare diseases by improving trial efficiency, but weaknesses can include difficulties in identifying bias and unexpected heterogeneity or effect size.

Ultimately, determining which patient will respond to which drug is the key to drug discovery in IPF. Optimizing clinical trials thus requires a comprehensive understanding of the pathophysiology of IPF, including identification of biomarkers that predict and quantify treatment response.

4. How progress in IPF genomics and other “omics” may inform drug development

Rapidly expanding capacity for, and decreasing cost of, next-generation sequencing technologies has presented a unique opportunity to leverage genetic, genomic, and multi-omic datasets for the pursuit of novel therapeutic targets for IPF and other chronic ILDs.

4.1 Genetic susceptibility to IPF

The role of genetic factors in determining susceptibility to IPF is well established, and inherited factors have been estimated to contribute at least one-third of all IPF risk (Fingerlin et al 2013). Multiple studies now demonstrate that both common (e.g., polymorphisms), and rare/ultra-rare (e.g., mutations) genetic variants are important determinants of IPF risk. Genome-wide association studies have implicated more than 15 common genetic variants as risk factors for IPF (Fingerlin et al 2013; Noth et al 2013; Allen et al 2017; Moore 2019), the most prominent of which is a polymorphism in the promoter region of the gene encoding for the airway mucin *MUC5B* (Seibold et al 2011; Zhang et al 2011). Compared to other IPF patients, those who carry the *MUC5B* T allele (which increases IPF risk) develop later onset and less rapidly progressive disease (Peljto et al 2013). Common genetic variants within toll interacting protein, an important regulator of innate immune responses (Zhu et al 2012), have also been associated with IPF susceptibility and prognosis (Noth et al 2013). Moreover, rs3750920, a functional synonymous coding variant that is located within toll interacting protein exon 3, has been associated with different response to N-acetylcysteine (NAC) (Oldham et al 2015). Specifically, NAC therapy was associated with improved survival

among subjects carrying an rs3750920 TT genotype but with a trend towards worse survival among those with a CC genotype. If confirmed, these findings would suggest that genetic makeup of individuals with IPF might influence their response to treatment.

Initial studies focused on familial cases of IPF implicated variants in genes related to surfactant processing (Thomas et al 2002; van Moorsel et al 2010; Wang et al 2009; Ono et al 2011) and telomere biology (Armanios et al 2007; Tsakiri et al 2007; Kropski et al 2014; Alder et al 2015; Stuart et al 2015; Cogan et al 2015; Kropski et al 2017; Borie et al 2016). It is now clear that compared to other IPF patients, those with severely shortened peripheral blood telomeres and/or known telomere pathway mutations have earlier-onset and more rapidly progressive disease (Newton et al 2016; Newton et al 2019; Stuart et al 2014). More recently, whole-exome (Petrovski et al 2017; Coghlan et al 2014) and whole-genome-sequencing studies (Dressen et al 2018) have suggested similar patterns of rare genetic variants in sporadic IPF patients. Together, these studies have yielded three major insights: 1) the genetic risk architecture in familial vs. sporadic IPF is similar; 2) IPF risk genes are predominantly expressed in the lung epithelium; and 3) there are likely multiple, genetically distinct IPF endotypes.

Investigation into the functional consequences of IPF-associated genetic variations has led to unexpected convergences that may inform key mechanisms underlying the pathogenesis of IPF. For example, many of the disease-associated surfactant protein mutations lead to improper processing or trafficking of pro-surfactant protein C, which leads to accumulation of misfolding proteins and activation of the unfolded protein response (UPR) (Mulugeta et al 2005; Lawson et al 2011), but it was soon recognized that epithelial UPR activation was a far more prevalent feature of IPF lungs (Korfei et al 2008; Lawson et al 2008) than could be explained by the frequency of surfactant protein mutations. More recently, it has been demonstrated that the *MUC5B* risk (T) allele (carried by >60% of IPF patients) may contribute to a feed-forward cycle of UPR activation, and escalating *MUC5B* production is regulated through the UPR-induced alternative splicing of the transcription-factor X-box-protein-1 (Chen et al 2019). In contrast, mutations in telomere-related genes have generally been associated with activation of telomere-DNA damage responses (Alder et al 2015; Chen et al 2015; Naikawadi et al 2016), which can trigger apoptosis or senescence of progenitor cells in the lung epithelium. These genotype-specific disease mechanisms conceptually lend themselves to precision medicine approaches, and underscore the need to consider genetic stratification in preclinical models and in clinical trials of emerging therapeutics.

4.2 Single-cell biology in IPF

The emergence of innovative microfluidic technologies that enable simultaneous profiling of the gene expression programs of thousands of individual cells (single-cell RNA-sequencing, scRNA-seq) (Macosko et al 2015; Klein et al 2015) has led to renewed interest in the use of genomic approaches to elucidate disease mechanisms. There have now been several studies using scRNA-seq in IPF lung tissue, and together they have led to important new insights into disease pathobiology (Xu et al 2016; Reyfman et al 2019; Habermann et al 2020; Adams et al 2020). Among the most striking findings to date are the emergence of cell-states/types in the IPF lung that are rarely observed in the healthy lung. Notable examples of

this include a Secreted Phosphoprotein 1 (osteopontin) expressing interstitial macrophage population (Reyfman et al 2019), a Collagen type 15, α -1 expressing peribronchiolar endothelial cell population (Adams et al 2020), a highly-activated fibroblast population characterized by high expression of hyaluronan-synthase-1 (Habermann et al 2020), and a basal-like-cell population expressing a combination of basal cell, alveolar, and mesenchymal programs (Habermann et al 2020; Adams et al 2020).

There are several immediately evident implications for antifibrotic drug development. While fibroblasts are the primary effectors cells that produce the pathologic ECM that is the hallmark of the IPF lung, these datasets have demonstrated that a diversity of fibroblast populations are actively producing pathologic ECM in IPF lungs (Habermann et al 2020; Adams et al 2020; Morse et al 2019). In addition to the well-studied activated myofibroblasts, several other fibroblast populations lacking actin alpha 2/alpha-smooth muscle actin expression and characterized by distinct surface markers, growth-factors/chemokine receptors, and spatial localization are found in the IPF lung. A key implication of this is that an antifibrotic therapy targeting mechanisms only relevant to one of these fibroblast subtypes will likely have a ceiling to its potential efficacy; combination therapies or those targeting mechanisms conserved across fibroblast subtypes may be required for maximal therapeutic benefit. Second, these basal-like cells (“KRT5-/KRT17+” or “aberrant basaloid”) (Habermann et al 2020) represent a previously undescribed cell state that could be therapeutically targeted. These cells are found immediately overlying regions of most active collagen production (Habermann et al 2020), produce collagen and fibronectin themselves, and express TGF- β , connective-tissue growth factor, and a number of other molecular drivers of fibroblast activation (Habermann et al 2020; Adams et al 2020). The origin of these cells is not certain; however, studies using organoid models and genetic lineage tracing indicate that a transcriptomically similar cell program characterizes an intermediate stage of AT1 cell differentiation (Kobayashi et al 2020). Together, these data suggest that failure of AT1 maturation may lead to an accumulation of cells “stuck” in a transitional state that produce key mediators of fibroblast activation through paracrine signaling mechanisms, consistent with data from several mouse models in which AT1 cell differentiation is impaired (Yao et al 2020; Wu et al 2020). Therapies interrupting these signaling loops could hold promise as novel therapeutic strategies. In addition to providing new mechanistic targets for IPF therapies, these high-resolution scRNA-seq datasets can be utilized to advance ongoing therapy development. For example, understanding the cell-type-specific expression profile of the target of a given therapy can be utilized to rationally choose potential biomarkers reflecting target engagement. A role of transcriptomics in ILD diagnosis has been established (Kim et al 2015), and shows promise for prediction of disease outcomes (Herazo-Maya et al 2017). Extension of these and similar approaches to prediction of therapeutic response seems a natural next step.

5. Pharmacological treatment

At present, there is no treatment that can cure IPF. Two drugs, pirfenidone and nintedanib are able to slow disease progression, but neither drug improves or even stabilizes lung function, or improves quality of life, and both therapies have tolerability issues (Kreuter et al 2015).

5.1 Pirfenidone

Pirfenidone (5-methyl-1-phenylpyridin-2[1H]-one) is an orally available, synthetic compound that exerts anti-fibrotic, anti-inflammatory and antioxidant properties through down-regulation of key pro-fibrotic growth factors including TGF- β ; inhibition of inflammatory cytokines (e.g., tumor necrosis factor- α) production and release; and reduction of lipid peroxidation and oxidative stress (Iyer et al 1999). Four phase 3 trials have evaluated the efficacy of pirfenidone in patients with IPF (Taniguchi et al 2010; Noble et al 2011; King et al 2014). Overall, these trials showed that pirfenidone slows down disease progression and functional decline in patients with IPF. In addition, pooled analyses and meta-analyses of clinical trials in IPF showed that pirfenidone treatment is associated with a reduced risk of mortality (Nathan et al 2017). Common adverse effects of pirfenidone include gastrointestinal intolerance (e.g., nausea, diarrhea and dyspepsia) and skin reactions (e.g., rash and photosensitivity), which are generally mild to moderate in severity and reversible following dose reduction or temporary drug discontinuation.

5.2 Nintedanib

Nintedanib is an intracellular inhibitor of vascular endothelial growth factor receptor 1–3, fibroblast growth factor receptor 1–3, and platelet-derived growth factor receptor α and β (Wollin et al 2015). By inhibiting these tyrosine kinase receptors, nintedanib interferes with a number of processes that have been implicated in the pathogenesis of IPF, including proliferation and migration of lung fibroblasts, and differentiation of fibroblasts to myofibroblasts. Two parallel 52-week, phase 3 trials consistently showed that nintedanib treatment, compared to placebo, was associated with a significantly reduced risk of disease progression (Richeldi et al 2014). Nintedanib appears also to have a mortality benefit (Canestaro et al 2016). The most frequent side effects associated with nintedanib use are diarrhea (reported by approximately 60% of patients within the first 3 months of treatment) and nausea, which in most cases are of mild or moderate intensity and manageable (Richeldi et al 2014).

6. A novel approach to treatment of IPF – the stem cells

Mesenchymal Stem Cells (MSCs) represent multipotent cells that are easily harvested from many tissues such as adipose tissue, peripheral blood, bone marrow and umbilical cord (Tzouveleakis et al 2018). Several lines of experimental evidence suggest strong anti-fibrotic, anti-inflammatory and immunomodulatory effects for MSCs both through paracrine signaling and potent differentiation capacity (Ortiz et al 2003; Toonkel et al 2013; Germano et al 2009). In particular, pre-clinical studies demonstrated that administration of MSCs was associated with downregulation of TGF- β signaling, significant improvement in lung histopathology, extent of fibrotic lesions as assessed by Ashcroft score, lung collagen content, and reduced bronchoalveolar lavage neutrophilia (Kumamoto et al 2009; Moodley et al 2009; Gazdhar et al 2013). Despite relative enthusiasm, there are still major concerns on the therapeutic role of stem cells in IPF mainly arising from experimental data suggesting a detrimental role for MSCs within a pro-fibrotic microenvironment (Barczyk et al 2015).

A previous phase Ib study investigating endobronchial delivery of autologous adipose-derived stem cells in patients with IPF demonstrated an acceptable 5-years safety profile, improvement in parameters of health-related quality and 100% survival rate 2 years following first administration (Tzouvelekis et al 2013; Ntolios et al 2018). In addition, intravenous delivery of placental derived MSCs had an acceptable safety profile in patients with moderately severe IPF (Chambers et al 2014), and functional and morphologic indices, including six-minute walk test, forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide or computed tomography fibrosis score, showed no statistically significant decline during the first 6 months of follow-up (Hostettler et al 2017). Furthermore, the AETHER trial suggested that intravenous administration of allogeneic bone marrow -MSCs in patients with mild-to-moderate IPF (n=9) was safe and promising with regard to slowing down disease progression (Glassberg et al 2017). However, these conclusions should be interpreted with caution, as this study was underpowered for the detection of significant changes in FVC and diffusing capacity of the lung for carbon monoxide; in addition, 2/9 patients died from what appeared to be unrelated causes at 10 weeks and 29 weeks post-infusion, respectively. Results from a recently FDA approved phase Ib randomized, placebo controlled, clinical trial (ReCell) on safety and efficacy of multi-dose intravenous regimens of bone marrow-MSCs in patients with IPF, are greatly anticipated (Tzouvelekis et al 2018). Notably, all the studies on MSCs conducted thus far were severely underpowered and thus firm conclusions cannot be drawn.

Future studies on MSCs are hampered by the 2014 FDA approval of nintedanib and pirfenidone, leading to major delays or even failures to meet enrolment timelines. Finally, many unanswered questions remain with regard to the optimal route of administration (intravenous, endobronchial), the origin of stem cells (bone marrow, adipose- or placental-derived), frequency and dose of therapeutic regimens, and most importantly study design and phenotypic selection of patients (early or advanced disease) who are most likely to benefit from cell-based therapies. Selection of appropriate trial end-points is another important issue, as the majority of previous trials have relied on a minimum number of infusions and a short follow-up period that may limit the ability to identify and quantify meaningful clinical outcomes.

7. A novel approach to drug administration: the inhalation route

Current IPF treatments are administered orally while several compounds in development are given either subcutaneously or intravenously (Table 1; Figure 2). However, of all of the internal organs the lung is the most accessible to topical administration of therapy. Inhaled drugs are attractive for several reasons, the most important being that delivery of treatment directly to the lung has the potential to maximize therapeutic exposure in regions at greatest risk of disease progression, whilst minimizing systemic exposure and thus reducing the potential for adverse effects. Inhaled treatments are already the mainstay for obstructive lung disorders such as asthma and chronic obstructive pulmonary disease, but have been poorly studied in IPF. In part, this reflects concerns regarding the feasibility of delivering inhaled compounds to the distal airspace in lungs distorted by fibrosis. A recent study, using radiolabelled salbutamol, has confirmed that inhaled drug delivery in IPF is feasible but is impacted by severity of fibrosis and particle size (with the optimal size being close to 1.5

microns) (Usmani et al 2018). Another study of a novel compound targeting the integrin $\alpha v\beta 6$ used positron emission tomography imaging of the integrin to demonstrate effective delivery of the drug to regions of fibrosis (Maher et al 2020). Similarly, a study of an inhaled Galectin-3 inhibitor showed down regulation of the receptor in alveolar macrophages in a dose-dependent manner (Hirani et al 2017). However, the same study identified greater systemic absorption of the drug from the lungs of IPF patients compared with healthy controls. Overall, these data confirm that inhaled administration of drugs is feasible in IPF and that this route may be important in minimizing side effects for patients. This strategy has also been explored with existing anti-fibrotic drugs (Khoo et al 2020; Homma et al 2012). A small Japanese study of patients with advanced IPF suggested that combination therapy with inhaled NAC and oral pirfenidone might reduce the annual rate of decline in FVC and improve progression-free survival compared to pirfenidone alone (Sakamoto et al 2015). Conversely, a recent 48-week, open-label, phase 3 trial of Japanese patients with IPF (n=81) showed that combination treatment with inhaled NAC and oral pirfenidone was associated with more rapid decline in FVC compared to pirfenidone alone (Sakamoto et al 2020).

8. Translating preclinical evidence into effective therapies

The IPF literature is littered with negative clinical trials, with many different causes for these results. Early studies of potential IPF therapies suffered from imprecise definitions of major ILD subtypes, with incorrect diagnostic labels given to patients who we would now consider to have different diseases. This resulted in examples of patients with “IPF” who responded to immunomodulatory medications such as prednisone and azathioprine, which was historically a commonly accepted therapy of IPF (American Thoracic society, 2000). Subsequent studies showed significant harm from these same therapies when they were applied to well-characterized patients with what we now define as IPF (Idiopathic Pulmonary Fibrosis Clinical Research Network, 2012), suggesting that previous patients who reportedly benefitted from these therapies likely had other diagnoses (i.e., ILD secondary to connective tissue diseases or hypersensitivity pneumonitis). Ongoing and future studies of IPF are much more rigorous in ensuring a consistent phenotype that is intended to represent a distinct patient population.

Our understanding of IPF biology has also dramatically improved over the last two decades, further supporting abandonment of some therapeutic strategies that were previously assumed to be valid options. Identification of key pathways involved in IPF genesis and progression as described above has ushered in an era in which virtually all major clinical trials now target pathways that are central to IPF. Some of these trials include measurements of simple peripheral blood biomarkers that are intended to reflect disease activity and be responsive to disease modification; however, there is currently no such tool that provides this information for an available IPF therapy. This gap highlights the need for future studies to approach biomarker development and testing in a rigorous manner, with the hopes that this will allow shorter, smaller, and less costly early-phase clinical trials. An ideal biomarker for this purpose would be biologically plausible, able to distinguish IPF from healthy and diseased controls, correlate with disease severity, predict disease progression and response to treatment, and be modified by treatment, with all of these findings then externally validated in a distinct cohort. Although clinically useful biomarkers frequently do not possess all of

these features, identifying a biomarker that meets these goals would have incredible benefits for future drug development.

Given their financial costs and the burden placed upon participants, it is imperative that clinical trials pursue appropriate therapeutic targets with drugs that have a high likelihood of success. Fortunately, this is the case for many of the IPF clinical trials that are currently ongoing, and it therefore appears more likely than ever that we will soon have additional medication options for these patients. In addition to assessing more rational and biologically plausible drug targets, it is critical that these large, multinational, and rigorous trials are also used to learn more about the disease by ensuring that participants contribute clinical data and biological samples. This should ideally be done on a large scale and within an open science concept in order to facilitate the next generation of drug development.

9. Conclusions

In the last few years, the dynamic research activity in the pathogenesis of IPF has led to the identification of several therapeutic targets and the development of a large portfolio of novel compounds. Some of these molecules, which are currently being investigated in clinical trials, are likely to reach the clinic in the near future. Nevertheless, the prerequisite for the development of a real cure for IPF is a deeper understanding of the mechanisms underlying disease development.

Conflict of interest form

Dr Spagnolo reports personal fees and institutional grants from PPM Services, Boehringer-Ingelheim and Roche, and personal fees from Chiesi and Galapagos, outside the submitted work. Dr Kropski has received advisory board fees from Boehringer-Ingelheim and Janssen Pharmaceuticals, is on the scientific advisory board of APIE Therapeutics, and has research contracts with Genentech, all outside the submitted work. Dr Jones reports grants from Boehringer Ingelheim, outside the submitted work. Dr Lee has received grants from the NIH and Boehringer Ingelheim, and consulting fees from Galapagos, Boehringer Ingelheim, United Therapeutics, Eleven P15, and Bonac, outside the submitted work. Dr Maher has received grants and personal fees from GlaxoSmithKline R&D and AstraZeneca, and personal fees from Boehringer Ingelheim, Roche, Bayer, Samumed, Galapagos, Celgene, Indalo, Pliant, Blade Therapeutics, Respivant, Novartis and Bristol-Myers Squibb, outside the submitted work. Dr Maher has also received, via his institution, industry-academic funding from and has received consultancy or speakers' fees from Apellis. Dr Ryerson reports grant funding and personal fees from Boehringer Ingelheim and Hoffmann-La Roche, outside of the submitted work. Dr Rossi, Dr Tzouveleakis and Dr Karampitsakos have nothing to disclose.

Abbreviations

AECs	alveolar epithelial cells
AT1	alveolar type 1
AT2	alveolar type 2
ECM	Extracellular matrix
FF	fibroblastic foci
FVC	forced vital capacity
ILD	interstitial lung disease

IPF	idiopathic pulmonary fibrosis
MSCs	Mesenchymal Stem Cells
TGF-β	Transforming growth factor- β
UPR	unfolded protein response

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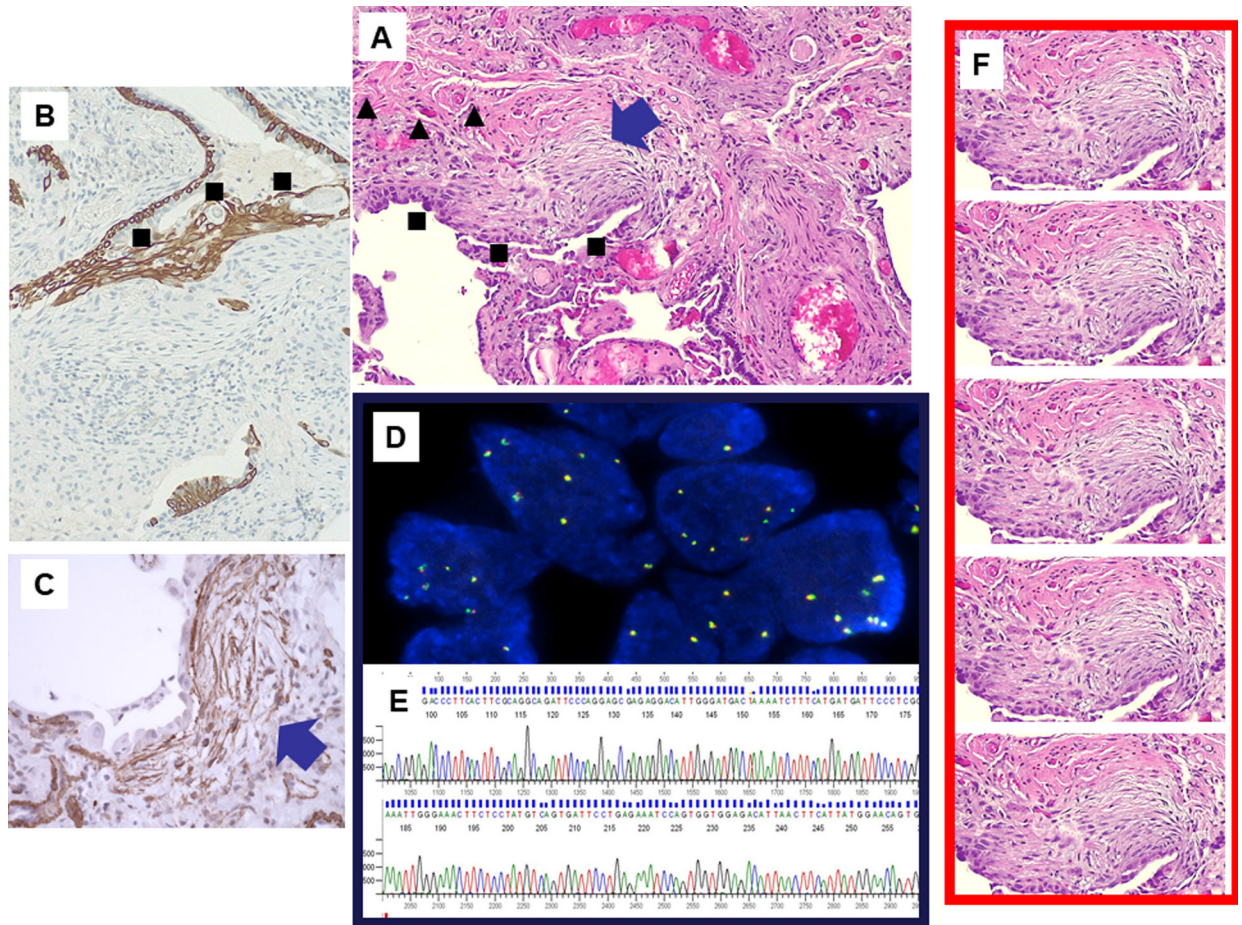


Figure 1.

Fibroblastic foci are discrete proliferations of myofibroblasts in myxoid stroma indicative of active fibrosis (blue arrow) often covered by activated alveolar epithelial cells representing the site of acute lung injury (squares) and with peripheral angiogenetic phenomena with multiple small capillaries (triangles) (A, hematoxylin-eosin stain). Fibroblastic foci may be investigated for protein expression by immunohistochemistry (B, up-regulation of c-MET in alveolar epithelial cells; squares; C, upregulation of the epithelial-to-mesenchymal transition protein Twist in myofibroblasts; arrow). Fluorescent in situ hybridization analysis of c-MET (D) and molecular investigation of c-MET mutations (electropherogram, E). Microdissection of fibroblastic foci from transbronchial biopsy allows obtaining an adequate amount of DNA/RNA for selective multiplex genomic and proteomic analysis (F).

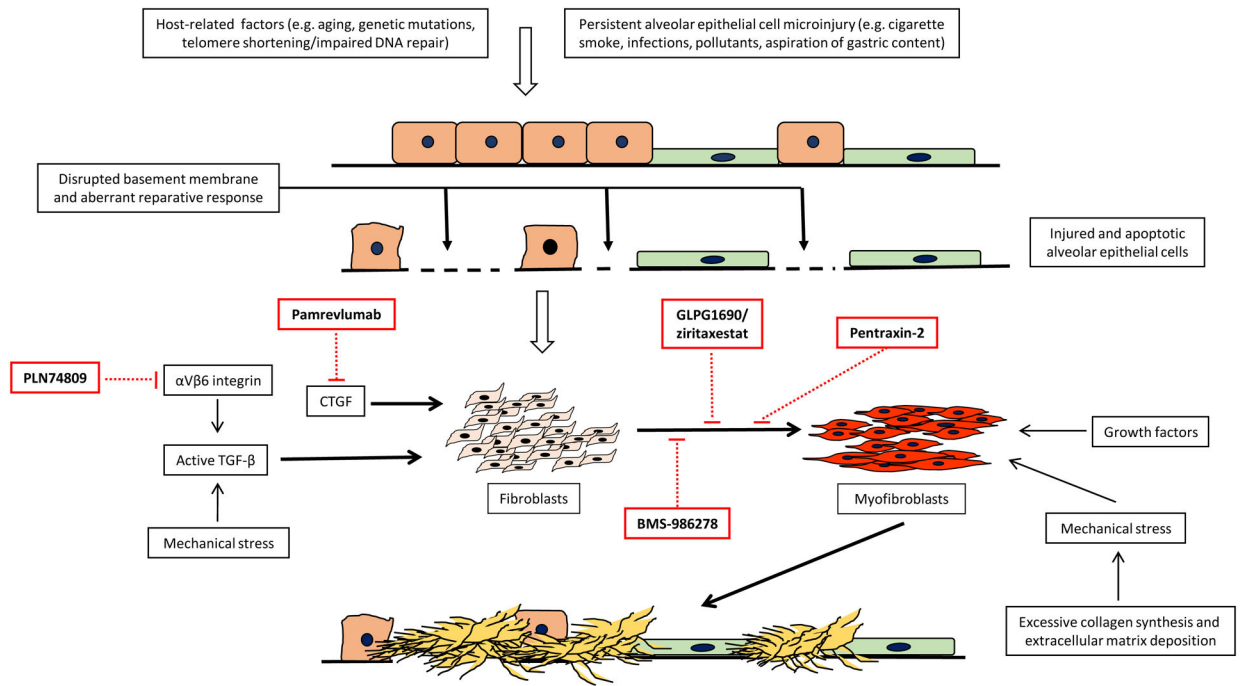


Figure 2.
Selected potential targets in IPF

Table 1.

Selected list of experimental treatments for idiopathic pulmonary fibrosis

Treatment	Mechanism of action	Phase/Study design	Status	Primary outcome	Trial identifier
DRUGS TARGETING FIBROBLASTS					
GLPG1690/ziritaxestat	Autotaxin inhibitor; oral	Phase III; randomized, double-blind, parallel-group, placebo-controlled	Recruiting	Rate of decline in FVC from baseline to week 52	NCT03733444 NCT03711162
Pamrevlumab	Fully human monoclonal antibody against CTGF; intravenous	Phase III, randomized, double-blind, placebo-controlled	Recruiting	Change in FVC (litres) from baseline to week 52	NCT03955146
Pamrevlumab	Fully human monoclonal antibody against CTGF; intravenous	Phase III, randomized, double-blind, placebo-controlled	Recruiting	Proportion of subjects with disease progression (absolute FVC percentage predicted decline 10% or death) from baseline to week 52	NCT04419558
TDI39	Galectin-3 inhibitor; inhaled	Phase IIb, randomized, double-blind, parallel, placebo-controlled	Recruiting	Rate of decline in FVC (mL) from baseline to week 52	NCT03832946
PLN-74809	Dual selective inhibitor of $\alpha_v\beta_1/\alpha_v\beta_6$ inhibitor; oral	Phase IIa, randomized, double-blind, dose-ranging, placebo-controlled	Recruiting	Number of participants with treatment-related AEs and laboratory abnormalities	NCT04396756
PLN-74809	$\alpha_v\beta_1$ and $\alpha_v\beta_6$ selective inhibitor; oral	Phase IIa, randomized, sequential assignment	Recruiting	Number of participants with a change from baseline in $\alpha_v\beta_6$ receptor occupancy as measured by PET	NCT04072315
BMS-986278	LPA antagonist; oral	Phase II, randomized, double-blind, placebo-controlled	Recruiting	Rate of change in percentage predicted FVC from baseline to week 26	NCT04308681
Jaktinib Dihydrochloride Monohydrate	JAK 1, JAK 2 and JAK 3 inhibitor; oral	Phase II, randomized, double-blind, placebo-controlled	Recruiting	Change in FVC from baseline to week 24	NCT04312594
Saactinib	Highly selective Src tyrosine kinase family inhibitor; oral	Phase Ib/IIa, randomized, double-blind, parallel design, placebo-controlled	Recruiting	Safety, tolerability, pharmacokinetics, pharmacodynamics, efficacy (as measured by change in FVC from baseline to week 24)	NCT04598919
DRUGS TARGETING ALVEOLAR MACROPHAGES AND THEIR MEDIATORS					
rhPTX-2/PRM-151	TGF- β 1 modulator; intravenous	Phase III, randomized, double-blind, placebo-controlled	Recruiting	Absolute change in FVC (mL) from baseline to week 52	NCT04552899
rhPTX-2/PRM-151	TGF- β 1 modulator; intravenous	Phase III, open-label extension study	Recruiting	Incidence and severity of AEs, and infusion related reactions; percentage of participants permanently discontinuing study treatment due to AEs	NCT04594707
IMMUNOTHERAPIES					
VAY736/ianalunab	IgG1 monoclonal antibody against BAF1 receptor; subcutaneously	Phase II; randomized, subject-, investigator-, sponsor-blinded, placebo-controlled	Recruiting	Change from baseline to week 48 in FVC	NCT03287414
GLPG1205	GPR84 antagonist; oral	Phase II; randomized, double-blind, placebo-controlled	Completed (results pending)	Change in FVC from baseline to week 26	NCT03725852

Treatment	Mechanism of action	Phase/Study design	Status	Primary outcome	Trial identifier
DRUGS TARGETING BROAD PATHWAYS/SIGNALING					
KD025/SLx-2119	ROCK2 inhibitor; oral	Phase II, open label	Active, not recruiting	Change in FVC from baseline to week 24; number of subjects experiencing AEs	NCT02688647
ND-L02-s0201/BMS-986263	HSP47 inhibitor; intravenous	Phase II, randomized, double-blind, placebo-controlled	Recruiting	Number of patients with treatment-related AEs from baseline to week 24	NCT03538301
CC-90001	Selective JNK inhibitor; oral	Phase II, randomized, double-blind, placebo-controlled	Recruiting	Change in percentage predicted FVC from baseline to week 24	NCT03142191
GKT137831/Setanaxib	NOX1 and NOX4 inhibitor; oral	Phase II, randomized, double-blind, placebo-controlled	Not yet recruiting	Surrogate biomarker of oxidative stress by mass spectrometry from baseline to week 24	NCT03865927
C21	Angiotensin type 2 receptor agonist; oral	Phase II, open-label, single-arm	Not yet recruiting	Nature and frequency of AEs occurring over the trial period	NCT04533022
SENOLYTICS					
Dasatinib + Quercetin	Elimination of senescent cells; oral	Phase I, randomized (some patients are randomized to placebo or study drug while others go into open label)	Completed (results pending)	Percentage of pro-inflammatory expressing cells in skin biopsy obtained at baseline and at week 4	NCT02874989
SMALL INTERFERING RNA					
TRK-250	Nucleic acid suppressing expression of TGF- β 1 protein at gene expression level; inhaled	Phase I, randomized, double-blind, placebo-controlled, single and multiple dose	Recruiting	Incidence and severity of adverse events up to 7 days after last dose	NCT03727802
STEM CELLS					
Human autologous lung stem cells	Immunomodulatory, anti-proliferative, and anti-inflammatory; intravenous	Phase I, randomized, open label	Recruiting	Number of patients with AEs and serious AEs	NCT04262167
Human autologous lung stem cells	Immunomodulatory, anti-proliferative, and anti-inflammatory; injected by bronchoscopy	Phase I/Phase II, open label	Recruiting	Change in FVC from baseline to week 48	NCT02745184
UNDEFINED MECHANISM OF ACTION					
TD-1058	Undefined; inhaled	Phase I, randomized, double-blind, parallel-group, placebo-controlled	Recruiting	Number and severity of treatment emergent AEs	NCT04589260

Abbreviations: AE: adverse event; AUC: area under the curve; BAFF: B-cell activating factor; BAL: bronchoalveolar lavage; Cmax: maximum observed concentrations; CTGF: connective tissue growth factor; FVC: forced vital capacity; GPR84: G Protein-coupled Receptor 84; HSP: Heat-Shock Protein; JAK: Janus kinase; JNK: c-Jun N-terminal kinase; LPA: Lysophosphatidic acid; mTOR: mammalian target of rapamycin; NOX: Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase; pAKT: phosphorylated AKT; PD: pharmacodynamics; PET: positron emission tomography; PI3K: Phosphatidylinositol 3-kinases; ROCK: Rho-associated coiled-coil kinase; TGF- β 1: transforming growth factor β 1