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Targeted therapy for idiopathic pulmonary fibrosis: where to now?

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Abstract

Idiopathic pulmonary fibrosis (IPF) is an aging-associated recalcitrant lung disease with historically limited therapeutic options. The recent approval of two drugs, pirfenidone and nintedanib, by the United States Food and Drug Administration (FDA) in 2014 has heralded a new era in its management. Both drugs demonstrated efficacy in Phase III clinical trials by retarding the rate of progression of IPF; neither drug appears to be able to completely arrest disease progression. Advances in the understanding of IPF pathobiology have led to an unprecedented expansion in the number of potential therapeutic targets. Drugs targeting several of these are under investigation in various stages of clinical development. Here, we provide a brief overview of the drugs currently approved, and others in Phase II clinical trials. Future therapeutic opportunities that target novel pathways, including some that are associated with the biology of aging, are examined. A multi-targeted approach, potentially with combination therapies, and the identification of individual (or subsets of) patients who may respond more favorably to specific agents are likely to be more effective.

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive lung disease with high mortality and morbidity [1–3]. The world-wide prevalence of IPF continues to rise [4, 5]. Early disappointments with several anti-fibrotic agents [6–9] have led to clinical guidelines strongly recommending against use of most drugs previously studied [10]. Significant advances have been made in our understanding of the pathobiology of lung fibrosis [11–13]. These insights have led to an unprecedented expansion in the number of therapeutic targets that have undergone testing in clinical trials. Two drugs – pirfenidone and nintedanib – were approved by the United States Food and Drug Administration (FDA) in 2014. Here, we

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Compliance with ethical standards

Tracy Luckhardt participated in the advisory board for Intermune Inc. (manufacturer of pirfenidone) in June 2014 and received an honorarium and travel expenses.

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review data supporting the use of these drugs for the treatment of IPF, and look ahead to emerging drugs and novel therapeutic targets for this recalcitrant disease.

2. Aging as a paradigm in IPF pathogenesis

Our understanding of the pathogenesis of IPF has evolved over the past three decades, and the role of aging in this disease process is gaining greater attention [14, 15]. The diagnosis of IPF is typically made beyond the fifth decade of life, and there is an increase in both the incidence and prevalence of the disease with advancing age [4, 5, 16–18]. The biological hallmarks of aging [19], namely, genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis (including impaired autophagy), deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication, are being linked to key pathobiological processes in fibrosis [15].

Both clinicians and scientists intuitively approach fibrosis as a pathological process; however, it can be argued that fibrosis serves an adaptive host response function [20]. Accordingly, fibrosis may be viewed as a physiological response conserved through evolution to survive tissue injury, even at the cost of a loss in organ structure/function. This “trade-off” would be predicted to select fibrotic repair over “perfect” organ regeneration in environments of limited bioenergetic resources. Progressive fibrosis may occur when the normal bidirectional signaling between the epithelium and mesenchyme (fibroblasts) that coordinates repair becomes aberrant in the context of chronic injury and aging. This aberrant signaling may result from several factors such as elevated oxidative stress, impaired fibrinolysis, and alterations in cytokines, chemokines, growth factors, and eicosanoids [21]. Ultimately, the causes of pathological fibrosis likely involve impaired ability to clear antigens, autoimmunity, impaired regeneration, and the aberrant activation of developmental or wound healing genes [20]. In the context of aging, senescence of both the epithelium and mesenchyme may be predicted to give rise to cell phenotypes and fates that are characteristic of non-resolving fibrosis (Fig. 1). Consequently, the putative therapeutic targets are myriad and provide opportunity for a multipronged approach to intervene along a spectrum, from halting the progression of fibrosis to reversing remodeling to achieve normal organ structure and function.

3. Review of current drugs

3.1. Pirfenidone

About 3 years after its approval in Europe in 2011, pirfenidone has been approved by the United States FDA for the treatment of IPF. Two decades have passed since the first report in the mid-1990s of its potential efficacy in amelioration of experimental lung fibrosis in hamsters [22]. Since then, it has been studied extensively in several animal models and found to be effective in preventing/treating fibrosis involving the lungs, heart, liver, and kidneys [23]. Recent studies have employed local delivery of pirfenidone-containing nanoparticles to treat lung fibrosis in mice [24]. Interestingly, the precise mechanisms of action of pirfenidone that mediate anti-fibrotic effects *in vivo* are ill-defined, although purported to be via multiple pathways, including down-regulation of inflammatory cytokines

(such as tumor necrosis factor-α), pro-fibrotic cytokines (such as transforming growth factor-β, TGF-β), and oxidative stress [25].

In the large multicenter Phase III clinical (ASCEND) trial that ultimately led to the approval of pirfenidone in the U.S., treatment with the drug (compared to placebo) significantly reduced the decline in lung function (as measured by an absolute decrease in forced vital capacity, FVC) and exercise tolerance, and improved progression-free survival in patients with IPF [26]. In this study of 555 patients, 278 received pirfenidone, and 277 received placebo. While this trial failed to show a significant mortality benefit, pooling the data with earlier multicenter Phase III (CAPACITY) trials [27] revealed statistically significant reduction in all-cause mortality (hazard ratio 0.52), as well as IPF-related mortality (hazard ratio 0.32), in patients receiving pirfenidone.

The target dosing of pirfenidone is 2403 mg/day in 3 divided doses. Adverse effects are common with pirfenidone therapy. In the ASCEND trial, among patients receiving pirfenidone, 36% had nausea (vs. 13.4% placebo), and 28% had a rash (vs. 8.7% placebo). Other known adverse effects include upper gastrointestinal (GI) symptoms such as vomiting, dyspepsia and esophageal reflux, in addition to elevated hepatic enzymes, asthenia and weight loss [26, 27].

3.2. Nintedanib

Nintedanib is a multiple tyrosine kinase inhibitor known to inhibit the receptor tyrosine kinases of platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and vascular endothelial growth factor (VEGF) [28]. There are relatively fewer studies of the efficacy of nintedanib in pre-clinical animal models [29]. Originally used in trials to treat various cancers [30], nintedanib was studied in a Phase II (TOMORROW) trial for IPF [31]. Encouraging results from this trial formed the basis for larger Phase III (INPULSIS) trials that led to its approval for use in IPF in Europe and USA [32]. Recent studies have attempted to define the mechanisms of the anti-fibrotic action of nintedanib via its inhibitory effect on receptor tyrosine kinases leading to inhibition of fibroblast proliferation and migration, myofibroblast differentiation, extracellular matrix (ECM) synthesis, and inflammation [33, 34]. We have recently reported that nintedanib mediates other actions on fibroblasts, including induction of autophagy and direct inhibition of TGF-β receptor signaling [35].

In the two large multicenter INPULSIS trials, a total of 1061 patients with mild-moderate IPF (FVC of 50% or more of predicted; diffusion capacity of the lung for carbon monoxide, DLCO of 30–79% of predicted) were studied; 638 received nintedanib and 423 received placebo [32]. In both studies, nintedanib significantly decreased the rate of decline in FVC. Nintedanib also decreased the incidence of acute exacerbations in INPULSIS 2, but not in INPULSIS 1.

The dosing of nintedanib is at 300 mg/day in two divided doses. Adverse effects are common with Nintedanib therapy. In the INPULSIS trials, among patients treated with nintedanib, >60% reported diarrhea (vs. ~18% placebo). Other known adverse effects include elevated hepatic enzymes, and weight loss [32]. Overall, higher rates of drug

discontinuation due to adverse effects were noted in drug groups than placebo groups (21% vs 10.8% in INPULSIS 1, 17.6% vs 15.1% in INPULSIS 2).

3.3. Impact of the approved drugs on the treatment paradigm in IPF

Approval of pirfenidone and nintedanib has provided much needed options to treat patients with IPF. However, these come with a set of new questions and uncertainties. First, the criteria for selecting one drug over the other for a particular patient are unclear [36]. An informed decision-making process is necessary on the part of both physician and patient. In our experience, this decision is currently being driven primarily by the side-effect profile of each drug. Adverse effects leading to potential drug discontinuation has been considered in the 'conditional recommendation with moderate confidence in estimates of effect' for both drugs in the current guidelines for management of IPF [10]. Second, it is unknown if a combination of pirfenidone and nintedanib would confer added benefit over either drug alone. Third, among the other unknowns are the utility of either drug in patients with advanced IPF and/or advanced age with varied comorbidities. Fourth, there are concerns that the drugs may not be cost-effective, at least in the prevalent health-care delivery systems in some countries [37]. Lastly, these drugs will alter the design of future studies of newer drugs with the requirement for a new standard-of-care (control) arm in randomized clinical trials.

4. Drug targets/therapeutics in current clinical trials

Several newer agents are currently in Phase II clinical trials for IPF, and these are summarized in Table 1. Here, we discuss the rationale and important pre-clinical data that support the testing of these agents.

4.1. IL-13

Interleukin-13 (IL-13) is known to be increased in patients with IPF [38] and in animal models of aging-associated progressive fibrosis [39]. IL-13 signaling, via multiple mechanisms, including interplay with TGF-β and macrophage chemokine (C-C motif) ligand 2 (CCL2), drives fibrosis *in vitro* and *in vivo* [40–43]. Blocking IL-13 ameliorates experimental fibrosis in animal models [44]. IL-13 signaling axis has been a target of active investigation for pulmonary fibrosis with several anti-IL-13 monoclonal antibodies. A Phase II trial of QAX576 (NCT01266135, clinicaltrials.gov) was terminated with the cause yet unpublished. Two other Phase II randomized, double-blind, placebo controlled trials of monoclonal antibodies against IL-13, tralokinumab (NCT01629667) and lebrikizumab (NCT01872689) are ongoing. Of note, these two monoclonals are also being evaluated in Phase III trials for treatment of severe asthma. Interestingly, blocking the IL-13 receptor α2 (IL-13Rα2) appears to mediate pleiotropic effects in fibrosis. While studies support a pro-fibrotic role for IL-13Rα2 via TGF-β1 signaling [45], IL-13Rα2 may act as a decoy to IL-13 and thus diminish its pro-fibrotic effects [46].

4.2. CCL2

CCL2, also referred to as monocyte chemotactic protein 1 (MCP1), is purported to contribute to the pathogenesis of pulmonary fibrosis via multiple mechanisms, including effector functions downstream of IL-13 signaling [43, 47–49]. Interestingly, CCL2 has been

reported to mediate receptor-independent pleiotropic effects [50]. A Phase II clinical trial of anti-CCL2 monoclonal antibody Carlumab (CNTO888) in 126 IPF patients was completed recently, but found no evidence of benefit [51].

4.3. CTGF

Connective tissue growth factor (CTGF) is a matricellular protein that modulates cellular responses to the ECM. CTGF regulates fibroblast functions and mediates TGF-β actions on fibroblasts [52, 53]. In patients with IPF, CTGF expression is increased in bronchoalveolar lavage (BAL) fluid and in lung tissue, specifically type II alveolar epithelial cells and interstitial fibroblasts [54, 55]. In animal models of lung fibrosis, targeting CTGF diminishes fibrosis [56, 57]. A Phase II randomized, double-blind, placebo-controlled trial of CTGF-neutralizing antibody, FG-3019 (Fibrogen), is currently recruiting IPF patients (NCT01890265), with encouraging interim results from an earlier trial reported at the 2014 ATS Conference [58] As of 2014, out of 53 patients studied, 39 had completed the treatment period of 48 weeks; 27 of these had either no decrease or a modest decrease (< 5%) in FVC. In the 19 patients that accepted extended treatment, 9 had demonstrated improved or stable FVC through 81 weeks of treatment.

4.4. Lysyl Oxidase-like 2

Lysyl oxidases (LOX) are matrix cross-linking enzymes that catalyze formation of aldehydes from lysine residues in collagen and elastin. Their normal function helps stabilize the ECM to provide tensile strength to tissues [59, 60]. Increased activity of lysyl oxidase–like 2 (LOXL2) has been found to play a role in fibrotic disease; it is highly expressed in fibrotic regions of IPF lung, and its inhibition attenuates experimental lung fibrosis [61]. Serum LOXL2 has been noted to increase in patients with progressive IPF, suggesting its potential utility as a biomarker pending validation studies [62]. A Phase II trial (NCT01769196) in IPF using simtuzumab, a monoclonal antibody against LOXL2, is underway.

4.5. Integrin αvβ6

TGF-β signaling is central to fibrogenesis involving multiple organ systems [21, 63]. Global TGF-β inhibition may adversely affect its homeostatic functions, including immune suppression and tumor suppression [64]. The activation of latent TGF-β occurs locally in areas of fibrogenesis, and αvβ6 integrin is known to be an activator of such latent TGF-β complexes [65, 66]. Importantly, αvβ6 expression is minimal in normal lungs [66]. Lack of this integrin or loss of its function protects against experimental fibrosis in animal models [67, 68]. An ongoing Phase II study of STX-100, a monoclonal antibody against αvβ6, is currently recruiting patients (NCT01371305).

4.6. LPA1

Lysophosphatidic acid (LPA) is a phospholipid derivative that signals through multiple cell-surface G-protein coupled receptors that participate in pro-fibrotic wound-repair responses, such as fibroblast activation and resistance to apoptosis, epithelial cell apoptosis, and increased vascular permeability [69]. Inhibiting the LPA1 receptor has been shown to prevent fibrosis in various pre-clinical models [70–73]. Importantly, LPA levels are

increased in the BAL fluid of IPF patients; LPA1 signaling has potent fibroblast chemoattractant activity [71]. An ongoing Phase II study in IPF patients with BMS-986020, an LPA1 receptor antagonist, is currently recruiting patients (NCT01766817).

4.7. Autoantibodies

It has long been recognized that aging is associated with immunosenescence accompanied by an increase in autoantibodies [74, 75]. Recent pilot data indicate that targeting autoantibodies during acute IPF exacerbations might improve outcomes; strategies to reduce autoantibodies include treatment with rituximab, a monoclonal antibody against CD20 [76]. Studies have shown favorable effects on lung function in patients with scleroderma-induced interstitial lung disease with long term use of rituximab [77], despite concerns that rituximab treatment itself can induce lung fibrosis [78–80]. A Phase II study on Autoantibody Reduction Therapy in patients with Idiopathic Pulmonary Fibrosis (ART-IPF) is currently recruiting patients (NCT01969409).

4.8. Carbon Monoxide

Carbon monoxide is a gaseous molecule with multifunctional actions, and typifies contextual duplicity. While it is clearly toxic at high concentrations, therapeutic beneficial effects of exposure to lower concentrations are emerging in various conditions, including inflammation, sepsis, and acute lung injury [81–85]. Carbon monoxide suppresses *in vitro* fibroblast proliferation and bleomycin-induced lung injury in mice [86]. A Phase II multicenter trial to study inhaled carbon monoxide in IPF has recently stopped enrolling, and the results are yet to be published (NCT01214187).

4.9. Antimicrobials

Recent reports suggest that infections may contribute to IPF pathogenesis and lead to its progression, as well as acute exacerbations; however, precise cause-effect relationships have not been established [87–89]. There is also emerging interest in the role of the microbiome in IPF [87]. Use of antimicrobials to clear infection/colonization, thereby potentially altering the microbiome and the immune response, is being studied in IPF. In a study using the bleomycin-injury model in mice, azithromycin ameliorated lung fibrosis [90]. A randomized study of azithromycin in IPF is currently recruiting patients (NCT02173145), with the primary goal of assessing its immunomodulatory functions in suppressing cough. In a multi-center, randomized, controlled trial of cotrimoxazole in 181 IPF patients, in those patients adhering to regimen to study completion, drug therapy was noted to confer an all-cause mortality benefit (hazard ratio 0.21), and a reduction in need for increase in oxygen therapy (odds ratio 0.05), although no benefit in the primary outcome of retarding decline in lung function (FVC) or exercise capacity (6-minute walk test) [91]. In the cotrimoxazole group, while a significantly higher number of patients discontinued treatment due to adverse effects (chiefly nausea and skin rash), respiratory infections were significantly less in this group. A larger Phase III trial to test the validity of the treatment of IPF with cotrimoxazole (NCT01777737) is currently recruiting participants.

5. Emerging drug targets/therapeutic strategies

5.1. ROCK

First discovered in 1995 [92], the Rho kinase (ROCK) family members, ROCK1 and ROCK2, are serine/threonine kinases that regulate multiple cellular functions, including fibroblast apoptosis/survival and mechanotransduction [93, 94]. Many of their downstream targets are associated with the regulation of cytoskeletal stability, stress fiber formation, focal adhesion assembly, and cell contractility. Biomechanical stress-induced signal transduction by ROCKs may function as a feed-forward mechanism in the microenvironment of an already stiffened ECM in ongoing fibrosis. Recent studies have shown that inhibition of this pathway can ameliorate experimental fibrosis; more importantly, ROCK activity is known to be increased in areas of active fibrosis in human IPF, and thus, its inhibition may be an effective therapeutic strategy [95]. A Phase II study of an oral selective ROCK2 inhibitor, KD025, to treat IPF is being planned. It is noteworthy that this drug is being evaluated in multiple therapeutic areas, including autoimmune, fibrotic, neurologic, and metabolic diseases.

5.2. NOX4

NADPH oxidase 4 (NOX4) is an oxidant-generating enzyme that mediates myofibroblast activation and fibrogenic responses in multiple organ systems [96–101]. Its biochemical activity was first discovered as a TGF-β-responsive, H_2O_2-generating flavoenzyme in lung fibroblasts [102], several years prior to the identification and cloning of non-phagocytic NOX family enzymes [103]. NOX4 may demonstrate antagonistic pleiotropy in aging, contributing to excessive oxidative stress, thereby increasing predilection for fibrosis as a response to lung injury [104, 105]. Newer insights in epigenetics have helped better understand the mechanisms involved in NOX4 up-regulation in senescence [106]. Targeting NOX4 by intranasal siRNA as well as a small molecule inhibitor GKT137831, reverses the otherwise persistent fibrosis seen in aged mice [107]. Specific targeting of NOX4 awaits study in human IPF.

5.3. AMPK

AMP-activated protein kinase (AMPK) is a master metabolic sensor and homeostat at the cellular level. AMPK activation is among the few interventions which control the aging process and extend lifespan in animal models [108]. Interestingly, AMPK activation has been reported to mediate antifibrotic effects in experimental models, both *in vitro* and *in vivo*, although mechanisms are unclear [109]. AMPK activation leads to enhanced autophagy and metabolic reprogramming, both of which have potential therapeutic value in the context of aging-associated fibrosis [110, 111]. The antidiabetic drug, metformin, used by millions of people worldwide is a potent activator of AMPK, and being cost-effective with a favorable safety profile, is an attractive candidate for repurposing in IPF.

5.4. Other kinases

The concept of targeting protein kinases with tyrosine kinase inhibitors (TKIs) in IPF has been considered for several years [112–115]. The recent results with nintedanib suggest that

other TKIs may be as (or even more) effective, and this warrants further testing. In addition, while much has been studied and proposed about the role of receptor tyrosine kinases and their therapeutic targeting in pulmonary fibrosis [116, 117], the role of many non-receptor tyrosine- and serine-threonine kinases are unclear. Recent reports suggest that inhibition of the Src family of non-receptor protein kinases can ameliorate experimental fibrosis *in vitro* and *in vivo* [118]. Future studies are likely to inform if several kinase inhibitors that are either already approved or are being tested in treatment of various cancers maybe repurposed for IPF.

5.5. RNA inhibition

MicroRNAs (miRNAs) and small interfering RNAs (siRNAs) are tiny regulatory non-coding RNAs that have similar function but different sources of origin [119]. They decrease levels of target gene transcripts (mRNA) predominantly by mRNA destabilization, although they also modestly reduce translation efficiency [120]. Depending on the target(s) of the siRNA or miRNA, their activity can lead to a pro-fibrotic or anti-fibrotic milieu [121]. For example, miR-29 is known to have anti-fibrotic effects; its levels are suppressed by TGF-β stimulation *in vitro* and in lungs of bleomycin injured mice [122, 123]. On the other hand, miR-21 is known to promote fibrosis [124]. Strategies to increase levels of anti-fibrotic miRNAs/siRNAs and decrease levels of pro-fibrotic miRNAs would open up a multitude of potent and highly targeted options to treat IPF. Numerous miRNA-based therapeutics are already in development for various diseases such as HCV infection, various cancers, heart failure, and fibrosis [125]. Novel technologies for optimal delivery of siRNAs, miRNA mimics, and antimiR oligonucleotides are being explored [126].

6. Future directions

The year 2014 marks a watershed moment in the history of the care of IPF patients in the U.S. with the FDA approval of the first drugs ever for this disease. However, several questions regarding the use of pirfenidone and nintedanib remain. Can they benefit patients with more advanced disease than were enrolled in the Phase III studies? Can they be given in combination to achieve potentially greater efficacy? How long should either be given to patients who continue to progress despite treatment before they are deemed a treatment failure? Most importantly, given the inherent heterogeneity of IPF, how can we identify patients most likely to benefit from one or both of these drugs?

While the approval of pirfenidone and nintedanib should be considered an important landmark, much work needs to be done. With renewed interest and commitment from both academia and industry, several more drugs and drug targets are likely to follow. We have reviewed some of the emerging candidate drugs that are currently in Phase II trials, and several others that are in earlier stages of clinical or pre-clinical development. Deeper insights into the biology of aging in IPF pathogenesis are likely to uncover an exciting new set of drug targets. The repurposing of drugs has the potential to allow candidate drugs gain quicker access into the clinic. At the same time, drug discovery efforts based on emerging understanding of IPF pathobiology must continue. Coupling of drug discovery with biomarker discovery has the greatest potential to realize the promise of personalized

medicine. Discovery of biomarkers that serve as surrogates for clinically relevant end-points, ideally mortality, would facilitate clinical trials over shorter periods and potentially with fewer subjects. Ultimately, such advancements will result in bringing drugs with greater efficacy, safety, and tolerability to patients with IPF, a disease once thought to be a death-sentence.

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Key Points

Approval of pirfenidone and nintedanib has provided much needed options to treat patients with IPF.

Several new therapeutic agents are currently being studied in Phase II trials.

Advances in the understanding of IPF pathobiology have led to an unprecedented expansion in the number of novel therapeutic targets being investigated in pre-clinical studies.

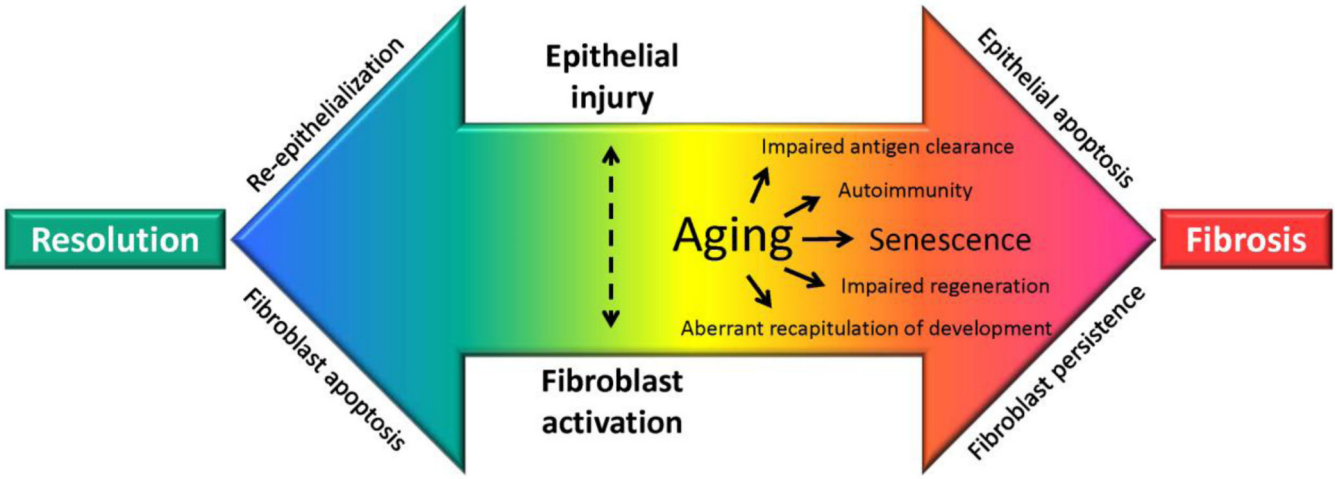

Figure 1. Proposed mechanisms for the predilection of fibrosis with aging

Aging may result in "immunosenescence" that results in impaired antigen clearance and autoimmunity; additionally, senescence of epithelial cells and fibroblasts result in impaired regeneration and aberrant recapitulation of developmental genes. These processes may perpetuate epithelial injury/apoptosis and fibroblast activation that results in failed re-epithelialization, fibroblast persistence and progressive fibrosis.

Table 1

Agents in current clinical trials for IPF

NCT, National Clinical Trial (www.clinicaltrials.gov)

Agent	Target	Purported mechanism of action	NCT Identifier
Tralokinumab	IL-13	Decreases expression of TGF-β and macrophage CCL2	NCT01629667
Lebrikizumab	IL-13	(as above)	NCT01872689
FG-3019	CTGF	Decreases CTGF-mediated pro-fibrotic actions on fibroblasts	NCT01890265
Simtuzumab	LOXL2	Decreases extracellular matrix cross-linking	NCT01769196
STX-100	Integrin αvβ6	Decreases activation of latent TGF-β	NCT01371305
BMS-986020	LPA1 receptor	Decreases vascular leak and fibroblast recruitment	NCT01766817
Rituximab	CD20	Decreases contribution of antibody-mediated autoimmunity	NCT01969409
Carbon Monoxide	Inflammation	Anti-inflammatory, may also suppress fibroblast proliferation	NCT01214187
Azithromycin	Bacteria, inflammation	Antimicrobial, immunomodulatory	NCT02173145
Cotrimoxazole	*Pneumocystis jiroveci*, bacteria	Antimicrobial	NCT01777737