Published in final edited form as:

Expert Opin Investig Drugs. 2010 June ; 19(6): 737–745. doi:10.1517/13543784.2010.484018.

Investigational approaches to therapies for idiopathic pulmonary fibrosis

Richard H. Gomer, Ph.D. [Professor of Biology] and

Texas A&M University, Biology MS 3258, College Station, TX 77843

Mark L. Lupher Jr., Ph.D. [Senior Vice President]

Discovery Research, Promedior, Inc. 371 Phoenixville Pike, Malvern, PA 19355

Abstract

Importance of the field—In fibrosing diseases, scar tissue begins to replace normal tissue, causing tissue dysfunction. For instance, in lung fibrosis, foci of what resembles scar tissue form in the lungs, impeding the ability of patients to breathe. These conditions represent a significant source of morbidity and mortality. More than 150,000 people in the US have some form of fibrotic lung disease, and the five-year mortality rate for these diseases can be as high as 80%. Despite this large unmet medical need, there are no FDA-approved therapies. Although our understanding of the causes and the biology of fibrosing diseases remains relatively poor, we have made impressive advances in identifying the major cell populations and many biochemical mediators that can drive this process. As a result, novel therapeutics are being developed based upon these discoveries.

Areas covered in this review—This review examines the experimental therapies currently under investigation as of late 2009 for a major class of lung fibrosis called idiopathic pulmonary fibrosis (IPF).

What the reader will gain—The reader will gain an overview of current experimental therapies for IPF.

Take home message—With the recent approval of Pirfenidone in Japan for use in IPF, and a rich pipeline of experimental therapies in various stages of clinical development, the future looks bright for new treatment options.

Keywords

Idiopathic pulmonary fibrosis; lung; fibrosis; fibroblast; fibrocyte; epithelial-mesenchymal transition

1. Introduction

Mammals have evolved a robust and rapid ability to form scar tissue in response to injury in order to contain the extent of damage. For instance, large wounds stimulate multiple sources of cells to produce granulation tissue in order to fill in the void. In addition to the proliferation of fibroblasts at the exposed surface of a wound, circulating monocytes can enter the wound and differentiate into fibroblast-like cells called fibrocytes [1-5]. Pericytes surrounding the microvasculature in and adjacent to the injury are rapidly stimulated to differentiate in

Phone 979 458 5745, Fax 979 845 2891, rgomer@mail.bio.tamu.edu.

Declaration of Interest

RH Gomer is a co-founder of, and ML Lupher is an employee of, Promedior Inc. Both authors have equity in and stock options from Promedior. This work was supported in part by NIH R01 HL083029.

fibroblast-like cells [6,7]. Finally, epithelial cells have also been described to differentiate into fibroblast-like cells *in vitro* and may participate in wound repair in a process termed epithelial-to-mesenchymal transition [8,9]. Having multiple sources of fibroblast-like cells then speeds the formation of the scar tissue and the closing of the wound. Unfortunately, having a strong and apparently hair-trigger capacity to respond to injury using multiple cell types has its drawbacks when they inappropriately form scar tissue.

Fibrosing diseases such as congestive heart failure, end stage kidney disease, and pulmonary fibrosis involve the inappropriate formation of scar tissue in an internal organ, and are associated with an estimated 45% of all deaths in the US [10]. There are at least 62 different fibrosing diseases, and there is no FDA-approved therapy [10]. In these diseases, insults to the tissue, such as ischemia in the heart or liver or particulate matter or toxins in the lungs, as well as unknown stimuli, initiate an apparently unnecessary scarring response. Fibroblast-like cells and extracellular matrix proteins such as collagen then begin to replace the normal tissue in an organ, leading to organ failure and death [10,11].

In the lung, fibrotic diseases include idiopathic pulmonary fibrosis (IPF) sarcoidosis and scleroderma with interstitial lung disease (SSc w/ILD). In addition, chronic severe asthma involves a fibrosis surrounding the airways, which tends then restrict the airways [12]. These conditions have a significant prevalence in the US compared to other serious medical conditions, and high mortality rates (Table 1). For example, 80% of IPF patients die within 5 years of diagnosis [13], and as with other fibrosing diseases, there are currently no FDA-approved anti-fibrotic therapeutics to treat this pathology. Even oxygen therapy fails to improve outcome [14].

In this review, we will discuss the current state of development of therapies for IPF. Patients typically first notice that they are getting shortness of breath when they exercise. Since many conditions can cause shortness of breath, determining that a patient has IPF is somewhat difficult. Clinical criteria and radiological examination using high-resolution computed tomography can be used for the diagnosis [15]. A lung biopsy showing foci of fibroblast-like cells and collagen can be used for atypical cases, as well as for confirmation of the diagnosis (Figure 1).

A commonly-used animal model for pulmonary fibrosis is treatment of mice or rats with bleomycin [16]. Although the model does not completely mimic human pulmonary fibrosis (for instance the bleomycin-induced pulmonary fibrosis resolves with time), one advantage of the model is that it is relatively rapid; fibrosis appears in the lungs 7-14 days after treatment with bleomycin. For clinical studies, two key measurements are generally used. The first is mortality, and the second is lung function. The latter can be measured using either spirometry, where the patient takes a deep breath and exhales into a machine that measures airflow rate and volume as a function of time, or diffusing capacity, where the patient inhales a breath of air containing a known amount of tracer carbon monoxide, holds their breath for 10 seconds, and then exhales, and the amount of carbon monoxide remaining in the exhaled air is measured; this then measures the ability of the lung to exchange a gas from the air to the blood.

A puzzling aspect of IPF is that rather than a single origin, such as in a tumor, multiple foci of scar tissue generally appear throughout the lungs and new foci appear with the progression of the disease [17]. Possibly because of the significant differences between the physiology of normal lung cells and the physiology of the fibrotic scar tissue, there are changes in the levels of many different markers in the lungs of IPF patients [18]. Although it is unclear if a change in the levels of a protein or other factor are associated with the cause of the fibrosis or are a secondary effect, a number of potential mediators/biomarkers of disease are currently being investigated [19,20].

Idiopathic pulmonary fibrosis does not appear to involve classical inflammation such as occurs in rheumatic diseases like rheumatoid arthritis, and formal clinical trials or general clinical impressions and experience indicate that broad spectrum anti-inflammatory drugs, immunosuppressants, and immunomodulators such as corticosteroids, azathioprine, cyclophosphamide, prednisone, colchicines, and interferon γ -1b have little effect on disease progression in the majority of patients with IPF [21] [22] [14,23] [24]. However, it is important to note that these results do not imply that immune cells play no role in the progression of disease. They only indicate that non-specific therapeutics do not appear to appropriately modulate the pathology of the disease. For example, monocyte-derived populations and their derived products have been strongly associated with both fibrosis progression and resolution, including in the lung [11,25].

2. Therapeutics in Development

Based upon our current understanding of the key molecular events in fibrosis, and the poor response of IPF patients to a variety of existing drugs, several groups are trying new experimental therapeutics for the treatment of IPF (Table 2).

Pirfenidone

Pirfenidone is a small molecule drug administered orally, whose mechanism of action is currently unknown, and is under investigation for use in IPF by InterMune in the US (www.intermune.com) and by Shionogi in Japan (www.shionogi.co.jp/index_e.html). Pirfenidone inhibits collagen synthesis, down regulates the production of multiple cytokines, and blocks fibroblast proliferation and stimulation in response to cytokines in cell culture and in preclinical disease models. Pirfenidone has demonstrated activity in several experimental fibrotic conditions, including preclinical models of lung, kidney and liver fibrosis [26-41]. Pirfenidone is the only anti-fibrotic drug currently under investigation for the treatment of IPF to have successfully completed Phase 3 clinical testing. However, the results in the US studies were somewhat contradictory. Pirfenidone has been studied in multiple Phase 2 and three pivotal Phase 3 clinical trials for idiopathic pulmonary fibrosis (IPF) conducted by InterMune in the US and EU and by Shionogi in Japan. Shionogi sought and was granted regulatory approval in Japan in 2008 based upon a single initial Phase 3 study measuring changes in Forced Vital Capacity (FVC). InterMune has conducted two additional Phase 3 CAPACITY studies in the US and EU; however the results from the two studies were mixed. The primary endpoint of change in FVC at week 72 was not met in CAPACITY 1 ($p=0.501$), but was met with statistical significance in CAPACITY 2 ($p=0.001$), along with the secondary endpoints of categorical change in FVC and progression-free survival. Based upon these combined Phase 3 results, InterMune submitted an NDA for Pirfenidone to the US FDA in November of 2009.

Endothelin receptor antagonists (Bosentan, Ambrisentan, Macitentan)

Endothelin receptor antagonists have demonstrated anti-fibrotic activity in preclinical models of pulmonary fibrosis due to their ability to block fibroblast contraction of collagen fibers and ability to reduce fibroblast activation [42-44]. Bosentan is a small molecule dual endothelin receptor antagonist administered orally. Bosentan was previously approved by the FDA for use in the treatment of pulmonary arterial hypertension as TracleerTM. An initial Phase 2 study of Bosentan in IPF patients (the BUILD-1 study) did not meet its primary endpoint of change from baseline up to month 12 in exercise capacity, and Bosentan also failed to show efficacy in a similar BUILD-2 study in scleroderma/ILD patients. A Phase 3 study investigating the drug for efficacy in a selected subgroup of IPF patients with biopsy-proven IPF and little radiographic honeycombing also recently failed. Phase III trials of the endothelin receptor antagonists Ambrisentan (Gilead Sciences) and Macitentan (Actelion Pharmaceuticals) are currently underway.

N-Acetylcysteine (Fluimucil™)

N-Acetylcysteine (NAC), also known as Fluimucil™, is an amino acid supplement classified as a natural product which is administered orally. NAC was investigated for use in IPF by the Zambon Group, SA (www.clinicaltrials.gov). NAC increases levels of the anti-oxidant glutathione [45], which can protect tissues from oxidant induced damage, a potential side effect of the common use of azathioprine in IPF patients. A single Phase 3 study of NAC with prednisone and azathioprine compared to prednisone and azathioprine in IPF patients did meet its primary endpoint of vital lung capacity and single-breath carbon monoxide diffusing capacity (D_{LCO}) [46]. At one year, the decline in vital capacity was significantly less severe in those receiving NAC compared with those given placebo (relative difference: 9%, p<0.02). D_{LCO} also deteriorated less in those given NAC (relative difference: 24%, p=0.003). The NIH IPF net is currently conducting a three-arm Phase III trial (PANTHER-IPF) of NAC compared to a combination of NAC, azathioprine, and prednisone, or placebo.

Minocycline hydrochloride

Minocycline hydrochloride is a broad spectrum tetracycline antibiotic administered orally, which is being studied in an investigator-initiated Phase 3 clinical study of IPF patients (www.clinicaltrials.gov). In addition to its antimicrobial properties, minocycline has also demonstrated anti-inflammatory and anti-angiogenic effects in preclinical models and clinical studies [47]. Although this trial initiated in 2005, no results have been reported.

Sildenafil (Revatio™)

Sildenafil is a small molecule phosphodiesterase 5 (PDE5) inhibitor administered orally and is under investigation in IPF by Pfizer (www.pfizer.com). Sildenafil, although better known as the active ingredient in Viagra™ and approved for use in erectile dysfunction, is also approved under the trade name Revatio™ for the treatment of pulmonary arterial hypertension (PAH). Recent data have suggested that many patients with IPF have PAH [48], and PAH is associated with poor survival. An initial Phase 1/2 clinical trial demonstrated that Sildenafil could improve exercise tolerance in IPF patients with PAH [49]. A second small Phase 2 study by independent investigators was recently reported which did not show a significant difference in exercise tolerance between Sildenafil and placebo [50]. A larger Phase 3 study by Pfizer is currently ongoing and was scheduled to complete in 2009, but no results have been reported.

Thalidomide (Thalomid™)

Thalidomide is an anti-angiogenic and anti-inflammatory small molecule drug administered orally and is under investigation in IPF by Celgene (www.celgene.com). Thalidomide, which is sold as Thalomid™ for the treatment of multiple myeloma, has shown efficacy in preventing fibrosis in the bleomycin lung model [51] that correlated with reductions in interleukin-6 (IL-6), Transforming Growth Factor β (TGF- β) and vascular endothelial growth factor (VEGF) expression. An initial open label uncontrolled Phase 2 clinical trial was conducted in 19 IPF patients given 400 mg of oral thalidomide daily for 12 months. Results on lung function have not been presented from this trial, but a report indicating positive effects on reducing chronic cough in IPF patients has been presented [52], and a new Phase 3 clinical trial for the prevention and treatment of chronic cough in IPF has been initiated.

Imatinib mesylate (Gleevec™)

Imatinib mesylate, better known as Gleevec™, is a tyrosine kinase inhibitor administered orally and under investigation in IPF by Novartis (www.novartis.com). Imatinib mesylate was initially designed and approved for the treatment of chronic myeloid leukemia (CML), due to its potent inhibition of the bcr-abl tyrosine kinase, however it also potentially inhibits the PDGFR tyrosine kinase and the stem cell factor receptor c-kit tyrosine kinase. PDGF-mediated

fibroblast activation has been implicated in IPF [53], and imatinib mesylate inhibits preclinical models of pulmonary fibrosis [54-58]. An initial Phase 2 clinical trial was conducted in 120 IPF patients comparing 600 mg of imatinib mesylate to placebo, but the drug failed to improve survival or changes in forced vital capacity (FVC) [59]. A smaller Phase 2 clinical trial in SSc w/ILD patients recently completed with more positive results. 30 patients with severe SSc were given 400 mg of Gleevec daily. A presentation at the 2009 meeting of the American College of Rheumatology meeting indicated that after one year of treatment, the patients had improvements in lung function ranging from 9.6 to 11 percent as assessed by FVC and diffusion capacity.

Etanercept (Enbrel™)

Etanercept, better known as Enbrel™, is an anti-inflammatory biologic drug product administered by subcutaneous injection under investigation in IPF by Wyeth (www.wyeth.com). Etanercept is a soluble form of TNF α -receptor that blocks its interaction with ligand. TNF α in combination with IL-13 induces TGF- β production from monocytes, and etanercept administration significantly prevents fibrosis in the bleomycin model [60]. An initial randomized, prospective, double-blind Phase 2 clinical trial was conducted in 88 IPF patients comparing 25 mg twice weekly subcutaneous etanercept to placebo [61]. The primary endpoint was a change in percent predicted FVC and DLco over 48 weeks. Although there were no statistical differences in the predefined endpoints, a trend toward reduction in death or disease progression was observed in post hoc analysis.

Zileuton (Zyflo™)

Zileuton, also known as Zyflo™, is a 5-lipoxygenase (5-LO) inhibitor administered orally and under investigation in IPF by Cornerstone Therapeutics (formerly Critical Therapeutics, www.crtx.com). 5-LO is an enzyme responsible for converting arachidonic acid into the leukotrienes LTB4 and LTC4. These leukotrienes have inflammatory and fibrotic properties and are upregulated in the lungs of IPF patients [62]. Zileuton is currently approved for the treatment of asthma, and has also been shown to inhibit inflammation and fibrosis in the bleomycin model [63]. An initial Phase 2 clinical trial with a planned enrollment of 140 IPF patients comparing six months of treatment of zileuton to azathioprine/prednisone is currently ongoing. The primary endpoint of this trial is change in LTB4 levels in bronchoalveolar lavage fluid following six months of treatment. Secondary endpoints are progression free survival, change in dyspnea, change in quality of life, and change in physiology.

Tetrathiomolybdate (Coprexa™)

Tetrathiomolybdate, also known as *Coprexa*™, is a small molecule copper chelator administered orally and under investigation in IPF by Adeona Pharmaceuticals (formerly Pipex Therapeutics, www.adeonapharma.com). Tetrathiomolybdate complexes copper to protein and itself, rendering the copper unavailable for cellular uptake [64]. It was originally developed for Wilson's disease, and is also being developed as an anti-angiogenic agent for the treatment of cancer. Many angiogenic cytokines require normal levels of copper, and lowered copper levels reduce cytokine signaling while cellular copper requirements are met. Tetrathiomolybdate was shown to reduce fibrosis in the bleomycin model, and this effect was associated with inhibition of TNF α and TGF- β expression in lung homogenates [65,66]. An initial single-center, open-label, Phase 1/2 clinical trial was completed in 20 patients with IPF that had evidence of disease progression despite treatment with prednisone +/- cytotoxic therapy. The trial tested 20mg oral tetrathiomolybdate twice a day for 12 months. Primary endpoints were safety, percent FVC, DLco and exercise capacity (six minute walk distance), compared to baseline at 6 and 12 months. The only endpoint to reach statistical significance

was the relative appearance of ground glass under high resolution computed tomography (HRCT). The current status of this program is unknown.

BIBF-1120

BIBF-1120, also known as vargatef, is a tyrosine kinase inhibitor with specificity for VEGF, PDGF, and FGF receptor kinases. It is administered orally and under investigation in IPF by Boehringer Ingelheim (www.boehringer-ingelheim.com). BIBF-1120 is also being tested in parallel in a variety of cancer trials. A related analogue in the series, BIBF-1000 has demonstrated efficacy in reducing the severity of histopathology and fibrotic gene expression in the rat bleomycin model when dosing was initiated at day 10 [56]. However, collagen protein was not quantitated. A 12 month, double blind, randomized, placebo-controlled Phase 2 trial comparing the effect of BIBF-1120 administered at oral doses of 50 mg qd, 50 mg bid, 100 mg bid and 150 mg bid versus placebo in 432 patients with idiopathic pulmonary fibrosis is currently ongoing. The primary endpoint is the rate of decline in FVC, evaluated from baseline until 12 month of treatment, compared to placebo. Completion of the trial is expected in 2010.

CNTO-888

CNTO-888 is a monoclonal antibody targeting human chemokine ligand 2 (CCL-2), also known as monocyte chemoattractant protein 1 (MCP-1). It is administered by IV infusion and under investigation in IPF by Centocor (a division of J&J Pharmaceuticals, www.centocor.com). CNTO-888 is also being tested in parallel in a variety of cancer trials. Several studies have demonstrated an increase in the levels of CCL-2 in the BAL fluid of IPF patients relative to controls [67-70]. In addition, similar antibodies to CNTO-888 targeting the homologous murine proteins JE and MCP-5, when used in combination, have demonstrated efficacy in reducing fibrosis in the bleomycin model when dosed concurrent to injury [71]. A 48 week, double blind, randomized, placebo-controlled Phase 2 trial comparing the effect of CNTO-888 administered by IV infusion every 4 weeks of 1 mg/kg, 5 mg/kg, or 15 mg/kg versus placebo in 120 patients with idiopathic pulmonary fibrosis is currently ongoing. The primary endpoint is the rate of decline in pulmonary function, evaluated from baseline until 48 weeks of treatment, compared to placebo. Completion of the primary outcome of the trial is expected in 2012.

Octreotide

Octreotide is a somatostatin analog, and radiolabeled octreotide accumulates in the lungs of patients with IPF [72]. A Phase 2 trial of 30 mg octreotide injected IM every 4 weeks for 48 weeks in patients with IPF was started in France in 2006, with endpoints of lung function, lung appearance in HRCT, a 6 minute walking test, quality of life, and survival. Reports of this trial are not in the literature.

GC-1008

GC1008 is a pan-neutralizing IgG4 human antibody directed against all three isoforms of TGF- β . It is administered by IV infusion and under investigation in IPF by Genzyme (www.genzyme.com). TGF- β expression is increased in the lungs of patients with IPF relative to non fibrotic lung diseases and health controls [73]. *In vitro*, TGF- β is one of the most pro-fibrogenic cytokines known and *in vivo* is both necessary and sufficient for fibrotic disease induction and progression in many preclinical models including the bleomycin lung model [11]. GC-1008 has completed a Phase 1 open-label, multi-center, single-dose, dose-escalating trial, in 25 patients with idiopathic pulmonary fibrosis. Dose levels from 0.3 mg/kg to 8 mg/kg were investigated and the primary endpoints were safety, tolerability and pharmacokinetic of GC-1008. Although this trial was initiated in 2005 and completed in 2008 no formal results have been disclosed and no new trial in pulmonary fibrosis has been described.

FG-3019

FG-3019 is a human monoclonal antibody directed against Connective Tissue Growth Factor (CTGF). It is administered by IV infusion and under investigation in IPF by Fibrogen (www.fibrogen.com). CTGF is implicated in the pathogenesis of IPF and is considered a common pathway of various profibrotic processes [74] [75]. Preclinical models of lung fibrosis demonstrate that FG-3019 reduces scarring associated with CTGF and excess deposition of matrix components (www.fibrogen.com). FG-3019 has completed a Phase 1 open-label, single dose, sequential-group, dose-escalation study in 21 patients with idiopathic pulmonary fibrosis. Dose levels of 1 mg/kg, 3 mg/kg, and 10 mg/kg were investigated and the primary endpoints were safety, tolerability, pharmacokinetics, and immunogenicity of FG-3019. No dose limiting toxicities were reported. Although this trial was completed in 2004, no new trials in pulmonary fibrosis using FG-3019 have been described.

PRM-151

PRM-151 is a recombinant human form of serum amyloid P component (SAP). It is administered by IV infusion and under investigation in IPF by Promedior. PRM-151 specifically targets the monocyte cell population, irrespective of the profibrotic stimulus driving the pathology. *In vitro* data and *in vivo* data in preclinical models demonstrate that SAP is broadly effective at blocking the fibrotic process downstream of multiple types of injury and under multiple cytokine stimulation conditions [76-79] [80]. Promedior initiated a Phase 1 study with PRM-151 testing the safety and tolerability of increasing IV doses of PRM-151 in healthy volunteers and IPF patients in July of 2009. Results are expected in early 2010.

3. Conclusion

Idiopathic pulmonary fibrosis is a fibrosing disease of the lung with a high prevalence and high mortality rate, and no FDA-approved therapeutics. Work using both the bleomycin-induced pulmonary fibrosis rodent model, and studies on tissue from patients, has led to the development of a variety of possible therapeutics which are being tested in human clinical trials.

4. Expert opinion

The significant unmet medical need represented by fibrotic pulmonary diseases has attracted developers of a number of investigational therapeutics; however, most are at a very early stage of clinical development (Table 2). With few exceptions, each of these approaches targets inhibition of a single stimulatory agent. Given the large number of potential chemical mediators driving the fibrotic process in any given tissue, this functional redundancy will likely lead to sub-optimal efficacy with existing experimental therapies under investigation and potentially a requirement for combinatorial therapy similar to current practices in cancer. In addition, several of the cytokines and chemokines that are currently targeted, such as TGF- β , have additional beneficial properties in non-fibrotic tissues. As a result, systemic blockade of TGF- β activity leads to aberrant side effects in animal models and in human patients, further limiting the dosages allowable, and thereby potential efficacy. However, we are encouraged by the approval in Japan, and the possible approval in the US and Europe, of pirfenidone as a new therapeutic option for IPF, and we hope that more of the potential therapeutics described above will prove successful in treating, either alone or in combination, this terrible disease.

Acknowledgments

We thank Dr. Erica Herzog, Yale University School of Medicine, for Figure 1.

References

1. Paget, J. Lectures on Surgical Pathology Delivered at the Royal College of Surgeons of England. Wilson and Ogilvy; London: 1853.
2. Bucala R, Spiegel L, Chesney J, Hogan M, Cerami A. Circulating fibrocytes define a new leukocyte subpopulation that mediates tissue repair. *Mol Med* 1994;1:71–81. [PubMed: 8790603]
3. Chesney J, Bacher M, Bender A, Bucala R. The peripheral blood fibrocyte is a potent antigen-presenting cell capable of priming naive T cells in situ. *ProcNatlAcadSciUSA* 1997;94(12):6307.
4. Chesney J, Metz C, Stavitsky AB, Bacher M, Bucala R. Regulated production of type I collagen and inflammatory cytokines by peripheral blood fibrocytes. *JImmunol* 1998;160(1):419–25. [PubMed: 9551999]
5. Abe R, Donnelly SC, Peng T, Bucala R, Metz CN. Peripheral blood fibrocytes: differentiation pathway and migration to wound sites. *JImmunol* 2001;166(12):7556–62. [PubMed: 11390511]
6. Friedman SL. Mechanisms of hepatic fibrogenesis. *Gastroenterology* May;2008 134(6):1655–69. [PubMed: 18471545]
7. Lin SL, Kisseleva T, Brenner DA, Duffield JS. Pericytes and perivascular fibroblasts are the primary source of collagen-producing cells in obstructive fibrosis of the kidney. *Am J Pathol* Dec;2008 173(6):1617–27. [PubMed: 19008372]
8. Kalluri R, Weinberg RA. The basics of epithelial-mesenchymal transition. *J Clin Invest* Jun;2009 119(6):1420–8. [PubMed: 19487818]
9. Thiery JP, Acloque H, Huang RY, Nieto MA. Epithelial-mesenchymal transitions in development and disease. *Cell* Nov 25;2009 139(5):871–90. [PubMed: 19945376]
10. Wynn TA. Fibrotic disease and the T(H)1/T(H)2 paradigm. *NatRev Immunol* 2004;4(8):583.
11. Lupher ML Jr. Gallatin WM. Regulation of fibrosis by the immune system. *Adv Immunol* 2006;89:245–88. [PubMed: 16682276]
12. Schmidt M, Sun G, Stacey MA, Mori L, Mattoli S. Identification of circulating fibrocytes as precursors of bronchial myofibroblasts in asthma. *J Immunol* Jul 1;2003 171(1):380–9. [PubMed: 12817021]
13. Olson AL, Swigris JJ, Lezotte DC, Norris JM, Wilson CG, Brown KK. Mortality from pulmonary fibrosis increased in the United States from 1992 to 2003. *Am J Respir Crit Care Med* Aug 1;2007 176(3):277–84. [PubMed: 17478620]
14. Douglas WW, Ryu JH, Schroeder DR. Idiopathic pulmonary fibrosis: Impact of oxygen and colchicine, prednisone, or no therapy on survival. *Am J Respir Crit Care Med* Apr;2000 161(4 Pt 1): 1172–8. [PubMed: 10764308]
15. Schmidt SL, Sundaram B, Flaherty KR. Diagnosing fibrotic lung disease: when is high-resolution computed tomography sufficient to make a diagnosis of idiopathic pulmonary fibrosis? *Respirology* Sep;2009 14(7):934–9. [PubMed: 19740255]
16. Chua F, Gauldie J, Laurent GJ. Pulmonary fibrosis: searching for model answers. *Am J Respir Cell Mol Biol* Jul;2005 33(1):9–13. [PubMed: 15964990]
17. Hanak V, Ryu JH, de Carvalho E, Limper AH, Hartman TE, Decker PA, et al. Profusion of fibroblast foci in patients with idiopathic pulmonary fibrosis does not predict outcome. *Respir Med* Jun;2008 102(6):852–6. [PubMed: 18314323]
18. Konishi K, Gibson KF, Lindell KO, Richards TJ, Zhang Y, Dhir R, et al. Gene expression profiles of acute exacerbations of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* Jul 15;2009 180(2):167–75. [PubMed: 19363140]
19. Strieter RM, Mehrad B. New mechanisms of pulmonary fibrosis. *Chest* Nov;2009 136(5):1364–70. [PubMed: 19892675]
20. du Bois RM. Strategies for treating idiopathic pulmonary fibrosis. *Nat Rev Drug Discov* Feb;2010 9(2):129–40. [PubMed: 20094055]
21. Selman M, King TE, Pardo A. Idiopathic pulmonary fibrosis: prevailing and evolving hypotheses about its pathogenesis and implications for therapy. *Ann Intern Med* Jan 16;2001 134(2):136–51. [PubMed: 11177318]
22. Davies HR, Richeldi L. Idiopathic pulmonary fibrosis: current and future treatment options. *Am J Respir Med* 2002;1(3):211–24. [PubMed: 14720059]

23. Fiorucci E, Lucantoni G, Paone G, Zotti M, Li BE, Serpilli M, et al. Colchicine, cyclophosphamide and prednisone in the treatment of mild-moderate idiopathic pulmonary fibrosis: comparison of three currently available therapeutic regimens. *Eur Rev Med Pharmacol Sci Mar-Apr*;2008 12(2):105–11. [PubMed: 18575160]
24. King TE Jr, Albera C, Bradford WZ, Costabel U, Hormel P, Lancaster L, et al. Effect of interferon gamma-1b on survival in patients with idiopathic pulmonary fibrosis (INSPIRE): a multicentre, randomised, placebo-controlled trial. *Lancet Jul 18*;2009 374(9685):222–8. [PubMed: 19570573]
25. Prasse A, Muller-Quernheim J. Non-invasive biomarkers in pulmonary fibrosis. *Respirology Aug*; 2009 14(6):788–95. [PubMed: 19703061]
26. Brook NR, Waller JR, Bicknell GR, Nicholson ML. The experimental agent pirfenidone reduces pro-fibrotic gene expression in a model of tacrolimus-induced nephrotoxicity. *J Surg Res May 15*;2005 125(2):137–43. [PubMed: 15854665]
27. Iyer SN, Hyde DM, Giri SN. Anti-inflammatory effect of pirfenidone in the bleomycin-hamster model of lung inflammation. *Inflammation Oct*;2000 24(5):477–91. [PubMed: 10921510]
28. Oku H, Shimizu T, Kawabata T, Nagira M, Hikita I, Ueyama A, et al. Antifibrotic action of pirfenidone and prednisolone: different effects on pulmonary cytokines and growth factors in bleomycin-induced murine pulmonary fibrosis. *European journal of pharmacology Aug 20*;2008 590(1-3):400–8. [PubMed: 18598692]
29. Mansoor JK, Decile KC, Giri SN, Pinkerton KE, Walby WF, Bratt JM, et al. Influence of pirfenidone on airway hyperresponsiveness and inflammation in a Brown-Norway rat model of asthma. *Pulmonary pharmacology & therapeutics 2007*;20(6):660–8. [PubMed: 17049446]
30. Tian XL, Yao W, Guo ZJ, Gu L, Zhu YJ. Low dose pirfenidone suppresses transforming growth factor beta-1 and tissue inhibitor of metalloproteinase-1, and protects rats from lung fibrosis induced by bleomycin. *Chin Med Sci J Sep*;2006 21(3):145–51. [PubMed: 17086734]
31. Schelegle ES, Mansoor JK, Giri S. Pirfenidone attenuates bleomycin-induced changes in pulmonary functions in hamsters. *Proc Soc Exp Biol Med Dec*;1997 216(3):392–7. [PubMed: 9402144]
32. Kehrer JP, Margolin SB. Pirfenidone diminishes cyclophosphamide-induced lung fibrosis in mice. *Toxicol Lett Feb 7*;1997 90(2-3):125–32. [PubMed: 9067480]
33. Iyer SN, Wild JS, Schiedt MJ, Hyde DM, Margolin SB, Giri SN. Dietary intake of pirfenidone ameliorates bleomycin-induced lung fibrosis in hamsters. *The Journal of laboratory and clinical medicine Jun*;1995 125(6):779–85. [PubMed: 7539478]
34. Wang F, Wen T, Chen XY, Wu H. Protective effects of pirfenidone on D-galactosamine and lipopolysaccharide-induced acute hepatotoxicity in rats. *Inflamm Res Apr*;2008 57(4):183–8. [PubMed: 18344059]
35. Di Sario A, Bendia E, Macarri G, Candelaresi C, Taffetani S, Marzioni M, et al. The anti-fibrotic effect of pirfenidone in rat liver fibrosis is mediated by downregulation of procollagen alpha1(I), TIMP-1 and MMP-2. *Dig Liver Dis Nov*;2004 36(11):744–51. [PubMed: 15571005]
36. Kaibori M, Yanagida H, Yokoigawa N, Hijikawa T, Kwon AH, Okumura T, et al. Effects of pirfenidone on endotoxin-induced liver injury after partial hepatectomy in rats. *Transplantation proceedings Sep*;2004 36(7):1975–6. [PubMed: 15518716]
37. Kaibori M, Yanagida H, Uchida Y, Yokoigawa N, Kwon AH, Okumura T, et al. Pirfenidone protects endotoxin-induced liver injury after hepatic ischemia in rats. *Transplantation proceedings Sep*;2004 36(7):1973–4. [PubMed: 15518715]
38. Tsuchiya H, Kaibori M, Yanagida H, Yokoigawa N, Kwon AH, Okumura T, et al. Pirfenidone prevents endotoxin-induced liver injury after partial hepatectomy in rats. *Journal of hepatology Jan*; 2004 40(1):94–101. [PubMed: 14672619]
39. Garcia L, Hernandez I, Sandoval A, Salazar A, Garcia J, Vera J, et al. Pirfenidone effectively reverses experimental liver fibrosis. *Journal of hepatology Dec*;2002 37(6):797–805. [PubMed: 12445421]
40. Oku H, Nakazato H, Horikawa T, Tsuruta Y, Suzuki R. Pirfenidone suppresses tumor necrosis factor-alpha, enhances interleukin-10 and protects mice from endotoxic shock. *European journal of pharmacology Jun 20*;2002 446(1-3):167–76. [PubMed: 12098599]
41. Tada S, Nakamuta M, Enjoji M, Sugimoto R, Iwamoto H, Kato M, et al. Pirfenidone inhibits dimethylnitrosamine-induced hepatic fibrosis in rats. *Clinical and experimental pharmacology & physiology Jul*;2001 28(7):522–7. [PubMed: 11422218]

42. Schroll S, Arzt M, Sebah D, Nuchterlein M, Blumberg F, Pfeifer M. Improvement of bleomycin-induced pulmonary hypertension and pulmonary fibrosis by the endothelin receptor antagonist Bosentan. *Respiratory physiology & neurobiology*. Nov 28;2009
43. Mutsaers SE, Marshall RP, Goldsack NR, Laurent GJ, McAnulty RJ. Effect of endothelin receptor antagonists (BQ-485, Ro 47-0203) on collagen deposition during the development of bleomycin-induced pulmonary fibrosis in rats. *Pulmonary pharmacology & therapeutics* Apr-Jun;1998 11(2-3): 221–5. [PubMed: 9918760]
44. Park SH, Saleh D, Giaid A, Michel RP. Increased endothelin-1 in bleomycin-induced pulmonary fibrosis and the effect of an endothelin receptor antagonist. *American journal of respiratory and critical care medicine* Aug;1997 156(2 Pt 1):600–8. [PubMed: 9279246]
45. Atkuri KR, Mantovani JJ, Herzenberg LA. N-Acetylcysteine--a safe antidote for cysteine/glutathione deficiency. *Curr Opin Pharmacol* Aug;2007 7(4):355–9. [PubMed: 17602868]
46. Demedts M, Behr J, Buhl R, Costabel U, Dekhuijzen R, Jansen HM, et al. High-dose acetylcysteine in idiopathic pulmonary fibrosis. *The New England journal of medicine* Nov 24;2005 353(21):2229–42. [PubMed: 16306520]
47. Rempe S, Hayden JM, Robbins RA, Hoyt JC. Tetracyclines and pulmonary inflammation. *Endocr Metab Immune Disord Drug Targets* Dec;2007 7(4):232–6. [PubMed: 18220943]
48. Lettieri CJ, Nathan SD, Barnett SD, Ahmad S, Shorr AF. Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. *Chest* Mar;2006 129(3):746–52. [PubMed: 16537877]
49. Collard HR, Anstrom KJ, Schwarz MI, Zisman DA. Sildenafil improves walk distance in idiopathic pulmonary fibrosis. *Chest* Mar;2007 131(3):897–9. [PubMed: 17356110]
50. Jackson RM, Glassberg MK, Ramos CF, Bejarano PA, Butrous G, Gomez-Marin O. Sildenafil Therapy and Exercise Tolerance in Idiopathic Pulmonary Fibrosis. *Lung*. Dec 12;2009
51. Tabata C, Tabata R, Kadokawa Y, Hisamori S, Takahashi M, Mishima M, et al. Thalidomide prevents bleomycin-induced pulmonary fibrosis in mice. *J Immunol* Jul 1;2007 179(1):708–14. [PubMed: 17579094]
52. Horton MR, Danoff SK, Lechtzin N. Thalidomide inhibits the intractable cough of idiopathic pulmonary fibrosis. *Thorax* Aug;2008 63(8):749. [PubMed: 18663075]
53. Hetzel M, Bachem M, Anders D, Trischler G, Faehling M. Different effects of growth factors on proliferation and matrix production of normal and fibrotic human lung fibroblasts. *Lung* Jul-Aug; 2005 183(4):225–37. [PubMed: 16211459]
54. Li M, Abdollahi A, Grone HJ, Lipson KE, Belka C, Huber PE. Late treatment with imatinib mesylate ameliorates radiation-induced lung fibrosis in a mouse model. *Radiation oncology (London, England)* 2009;4:66.
55. Vuorinen K, Gao F, Oury TD, Kinnula VL, Myllarniemi M. Imatinib mesylate inhibits fibrogenesis in asbestos-induced interstitial pneumonia. *Experimental lung research* Sep;2007 33(7):357–73. [PubMed: 17849262]
56. Chaudhary NI, Roth GJ, Hilberg F, Muller-Quernheim J, Prasse A, Zissel G, et al. Inhibition of PDGF, VEGF and FGF signalling attenuates fibrosis. *Eur Respir J* May;2007 29(5):976–85. [PubMed: 17301095]
57. Aono Y, Nishioka Y, Inayama M, Ugai M, Kishi J, Uehara H, et al. Imatinib as a novel antifibrotic agent in bleomycin-induced pulmonary fibrosis in mice. *American journal of respiratory and critical care medicine* Jun 1;2005 171(11):1279–85. [PubMed: 15735062]
58. Daniels CE, Wilkes MC, Edens M, Kottom TJ, Murphy SJ, Limper AH, et al. Imatinib mesylate inhibits the profibrogenic activity of TGF-beta and prevents bleomycin-mediated lung fibrosis. *The Journal of clinical investigation* Nov;2004 114(9):1308–16. [PubMed: 15520863]
59. Daniels CE, Lasky JA, Limper AH, Mieras K, Gabor E, Schroeder DR. Imatinib Treatment for Idiopathic Pulmonary Fibrosis: Randomized Placebo-controlled Trial Results. *Am J Respir Crit Care Med* Mar 15;2010 181(6):604–10. [PubMed: 20007927]
60. Fichtner-Feigl S, Strober W, Kawakami K, Puri RK, Kitani A. IL-13 signaling through the IL-13alpha2 receptor is involved in induction of TGF-beta1 production and fibrosis. *Nature medicine* Jan;2006 12(1):99–106.

61. Raghu G, Brown KK, Costabel U, Cottin V, du Bois RM, Lasky JA, et al. Treatment of idiopathic pulmonary fibrosis with etanercept: an exploratory, placebo-controlled trial. *American journal of respiratory and critical care medicine* Nov 1;2008 178(9):948–55. [PubMed: 18669816]
62. Wilborn J, Bailie M, Coffey M, Burdick M, Strieter R, Peters-Golden M. Constitutive activation of 5-lipoxygenase in the lungs of patients with idiopathic pulmonary fibrosis. *J Clin Invest* Apr 15;1996 97(8):1827–36. [PubMed: 8621765]
63. Failla M, Genovese T, Mazzon E, Gili E, Muia C, Sortino M, et al. Pharmacological inhibition of leukotrienes in an animal model of bleomycin-induced acute lung injury. *Respir Res* 2006;7:137. [PubMed: 17118201]
64. Khan G, Merajver S. Copper chelation in cancer therapy using tetrathiomolybdate: an evolving paradigm. *Expert Opin Investig Drugs* Apr;2009 18(4):541–8.
65. Brewer GJ, Ullenbruch MR, Dick R, Olivarez L, Phan SH. Tetrathiomolybdate therapy protects against bleomycin-induced pulmonary fibrosis in mice. *J Lab Clin Med* Mar;2003 141(3):210–6. [PubMed: 12624602]
66. Brewer GJ, Dick R, Ullenbruch MR, Jin H, Phan SH. Inhibition of key cytokines by tetrathiomolybdate in the bleomycin model of pulmonary fibrosis. *Journal of inorganic biochemistry* Dec;2004 98(12):2160–7. [PubMed: 15541506]
67. Shinoda H, Tasaka S, Fujishima S, Yamasawa W, Miyamoto K, Nakano Y, et al. Elevated CC chemokine level in bronchoalveolar lavage fluid is predictive of a poor outcome of idiopathic pulmonary fibrosis. *Respiration; international review of thoracic diseases* 2009;78(3):285–92.
68. Car BD, Meloni F, Luisetti M, Semenzato G, Gialdroni-Grassi G, Walz A. Elevated IL-8 and MCP-1 in the bronchoalveolar lavage fluid of patients with idiopathic pulmonary fibrosis and pulmonary sarcoidosis. *American journal of respiratory and critical care medicine* Mar;1994 149(3 Pt 1):655–9. [PubMed: 8118632]
69. Capelli A, Di Stefano A, Gnemmi I, Donner CF. CCR5 expression and CC chemokine levels in idiopathic pulmonary fibrosis. *Eur Respir J* Apr;2005 25(4):701–7. [PubMed: 15802346]
70. Suga M, Iyonaga K, Ichiyasu H, Saita N, Yamasaki H, Ando M. Clinical significance of MCP-1 levels in BALF and serum in patients with interstitial lung diseases. *Eur Respir J* Aug;1999 14(2):376–82. [PubMed: 10515417]
71. Murray LA, Argentieri RL, Farrell FX, Bracht M, Sheng H, Whitaker B, et al. Hyper-responsiveness of IPF/UIP fibroblasts: interplay between TGFbeta1, IL-13 and CCL2. *The international journal of biochemistry & cell biology* 2008;40(10):2174–82.
72. Lebtahi R, Moreau S, Marchand-Adam S, Debray MP, Brauner M, Soler P, et al. Increased uptake of ¹¹¹In-octreotide in idiopathic pulmonary fibrosis. *J Nucl Med* Aug;2006 47(8):1281–7. [PubMed: 16883006]
73. Khalil N, O'Connor RN, Unruh HW, Warren PW, Flanders KC, Kemp A, et al. Increased production and immunohistochemical localization of transforming growth factor-beta in idiopathic pulmonary fibrosis. *American journal of respiratory cell and molecular biology* Aug;1991 5(2):155–62. [PubMed: 1892646]
74. Frazier K, Williams S, Kothapalli D, Klapper H, Grotendorst GR. Stimulation of fibroblast cell growth, matrix production, and granulation tissue formation by connective tissue growth factor. *J Invest Dermatol* Sep;1996 107(3):404–11. [PubMed: 8751978]
75. Lasky JA, Ortiz LA, Tonthat B, Hoyle GW, Corti M, Athas G, et al. Connective tissue growth factor mRNA expression is upregulated in bleomycin-induced lung fibrosis. *Am J Physiol* Aug;1998 275 (2 Pt 1):L365–71. [PubMed: 9700098]
76. Pilling D, Buckley CD, Salmon M, Gomer RH. Inhibition of fibrocyte differentiation by serum amyloid P. *J Immunol* Nov 15;2003 171(10):5537–46. [PubMed: 14607961]
77. Haudek SB, Xia Y, Huebener P, Lee JM, Carlson S, Crawford JR, et al. Bone marrow-derived fibroblast precursors mediate ischemic cardiomyopathy in mice. *Proc Natl Acad Sci U S A* Nov 28;2006 103(48):18284–9. [PubMed: 17114286]
78. Pilling D, Roife D, Wang M, Ronkainen SD, Crawford JR, Travis EL, et al. Reduction of bleomycin-induced pulmonary fibrosis by serum amyloid P. *J Immunol* Sep 15;2007 179(6):4035–44. [PubMed: 17785842]

79. Naik-Mathuria B, Pilling D, Crawford JR, Gay AN, Smith CW, Gomer RH, et al. Serum amyloid P inhibits dermal wound healing. *Wound Repair Regen* Mar-Apr;2008 16(2):266–73. [PubMed: 18318811]
80. Lin SL, Castano AP, Nowlin BT, Lupher ML Jr. Duffield JS. Bone marrow Ly6C^{high} monocytes are selectively recruited to injured kidney and differentiate into functionally distinct populations. *J Immunol* Nov 15;2009 183(10):6733–43. [PubMed: 19864592]
81. Raghu G, Weycker D, Edelsberg J, Bradford WZ, Oster G. Incidence and prevalence of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* Oct 1;2006 174(7):810–6. [PubMed: 16809633]
82. Robinson D Jr. Eisenberg D, Nietert PJ, Doyle M, Bala M, Paramore C, et al. Systemic sclerosis prevalence and comorbidities in the US, 2001-2002. *Curr Med Res Opin* Apr;2008 24(4):1157–66. [PubMed: 18430269]
83. McNearney TA, Reveille JD, Fischbach M, Friedman AW, Lisse JR, Goel N, et al. Pulmonary involvement in systemic sclerosis: associations with genetic, serologic, sociodemographic, and behavioral factors. *Arthritis Rheum* Mar 15;2007 57(2):318–26. [PubMed: 17330281]
84. Zureik M, Neukirch C, Leynaert B, Liard R, Bousquet J, Neukirch F. Sensitisation to airborne moulds and severity of asthma: cross sectional study from European Community respiratory health survey. *BMJ* Aug 24;2002 325(7361):411–4. [PubMed: 12193354]

Figure 1. Section of a lung from a patient with idiopathic pulmonary fibrosis

The section was stained with hematoxylin and eosin. A region of relatively normal lung is at upper right; the main mass of tissue in the center and lower left is fibrotic scar tissue that has replaced normal lung tissue. Figure is courtesy of Dr. Erica Herzog, Yale University School of Medicine, Internal Medicine - Pulmonary and Critical Care Division.

Table 1
Prevalence and 5 year mortality rates among fibrotic pulmonary diseases

Disease	Prevalence in the US	5 year mortality rate
Idiopathic Pulmonary Fibrosis	130,000	80%
Scleroderma with Interstitial Lung Disease	36,000	60%
Severe Chronic Allergic Asthma	440,000	50%

Data are from Raghu et al. [81] (idiopathic pulmonary fibrosis), Robinson et al. [82] and McNearney et al. [83] (Scleroderma with interstitial lung disease) and extrapolated from data on asthma in Europe for severe chronic allergic asthma [84].

Table 2
Anti-fibrotics in development for idiopathic pulmonary fibrosis

Company	Compound	Mechanism of action	Route	Status of project
Intermune; Shionogi	Pirfenidone	Unknown, reduces growth factors/ cytokines	Oral	Approved in Japan; Submitted in US and Europe
Gilead	Ambrisentan	Endothelin antagonist	Oral	Phase III
Actelion	Macitentan	Endothelin antagonist	Oral	Phase III
Zambon, NIH	N-Acetylcysteine	NFkB activation inhibitor; antioxidant	Oral	Phase III
UCLA (Wyeth)	Minocycline hydrochloride	Parp-1 inhibitor	Oral	Phase III
Pfizer	Sildenafil (Revatio)	PDE5 inhibitor	Oral	Phase III
Celgene	Thalidomide (Thalomid)	unknown, reduces collagen production	Oral	Phase III
Novartis	Imatinib mesylate (Gleevec)	Tyrosine kinase inhibitor	Oral	Phase II
Wyeth	Etanercept (Enbrel)	soluble TNF α receptor	Subcut.	Phase II
Cornerstone Therapeutics/ Skyepharma	Zileuton (Zyflo)	Leukotriene synthesis inhibitor; 5-LO inhibitor	Oral	Phase II
Adeona/Pipex Therapeutics	Tetrathiomolybdate (Coprexa)	copper chelator	Oral	Phase II
Boehringer Ingelheim	BIBF-1120 (Vargatef)	VEGFR, FGFR, PDGFR Inhibitor	Oral	Phase II
Centocor	CNTO-888	Anti-CCL-2 mAb	IV	Phase II
INSERM	Octreotide	Somatostatin analog	IM	Phase II
Genzyme	GC-1008	anti-TGF- β human monoclonal antibody	IV	Phase I
FibroGen	FG-3019	anti-CTGF human monoclonal antibody	IV	Phase I
Promedior	PRM-151	rhSAP, monocyte inhibitor	IV	Phase I

See text for details. Under Route, Subcut. indicates subcutaneous injection, IV indicates intravenous injection, and IM indicates intramuscular injection.