Chapter 23
Anti-Fibrotic Therapies from Other Organs: What the Gut Can Learn from the Liver, Skin, Lung and Heart

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Abstract Fibrosis and dysregulated healing can affect nearly every organ system in the body. Often fibrosis represents a final common pathway to end organ failure, and there is evidence for substantial conservation of the mechanisms of fibrosis across many or all of these organs. Given the significant and pervasive impact of fibrosis there is a clear need for effective anti-fibrotic therapies. The study of these mechanisms and therapies is a robust area of research and allows for exciting collaboration. The conservation of mechanisms effectively posits any therapy that demonstrates efficacy in one organ or model of fibrosis as being a potentially viable option in other organs as well. In this chapter we review the current state of anti-fibrotic therapies in organs other the intestine. There are exciting pipeline agents under investigation in multiple organs including the liver, lungs, kidney, skin, and heart. This chapter focuses on agents that are currently in clinical trials and have demonstrated promise as potentially reaching mainstream use.

Keywords Fibrosis · Inflammatory bowel disease · Intestinal fibrosis · Hepatic fibrosis · Pulmonary fibrosis · Renal fibrosis · Dermal fibrosis · Anti-fibrotic · Farnesoid X receptor · FXR · Obeticholic acid · Lysyl oxidase · LOX · Simtuzumab · Statin · Caspase · 5HT · CCR2 · CCR5 · GR-MD-02 · Peroxisome proliferator-activated receptor (PPAR) · Pirfenidone · Nintedanib · Tyrosine kinase inhibitor · mTOR · Lysophospholipid · Prostacyclin · αvβ6 · Endothelin · IL-13 · Connective tissue growth factor · Serum amyloid P · NADPH oxidase · NOX · Pyridoxamine · Janus kinase · JAK · TGF-β · Paquinimod · ACE inhibitor

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23.1 Introduction

The study of mechanisms of fibrosis and potential therapies is a rich area of investigation for numerous organs other than the intestine. Fibrosis is a final common pathway to organ failure in the liver, lungs, kidney, skin, and heart. Despite the diversity of tissues and functions, many mechanisms of fibrosis appear to be similar across organs [1–9]. Although the impact of fibrosis on human health is substantial, there is a stark paucity of therapies currently available to directly treat fibrosis, with the lung being the only organ to boast any approved therapies (Fig. 23.1, Table 23.1). However, there are candidate compounds targeting fibrosis across all of these organs that show promise. Given the conservation of pro-fibrotic mechanisms across tissues and organs, any therapy that effectively treats fibrosis in another organ warrants consideration and potentially investigation as a therapeutic for intestinal fibrosis as well [10]. This chapter will review the current state of anti-fibrotic therapy in the liver, lungs, kidney, skin, and heart, focusing on those agents currently in clinical trials and closer to mainstream use.

Many of these pathways and molecules have been studied in multiple organs. For the purposes of this chapter, we have divided the sections by organ. Each molecule

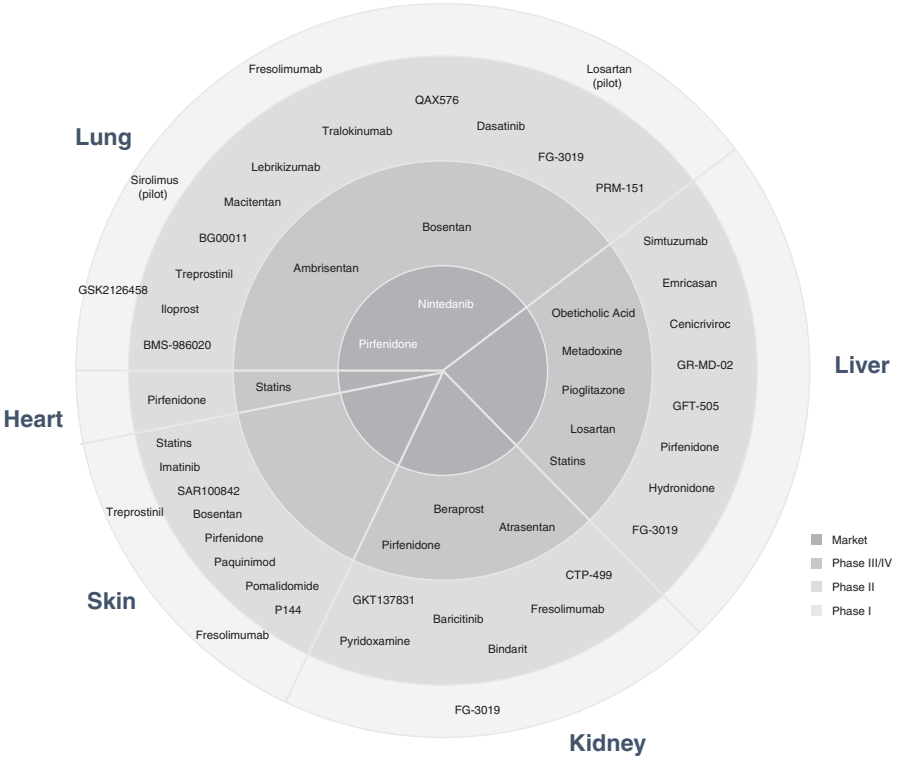

Fig. 23.1 Select anti-fibrotic agents by organ and clinical phase

Table 23.1 Select anti-fibrotic agents by organ and clinical phase

	Lung	Liver	Kidney	Skin	Heart
Market	• Pirfenidone				
	• Nintedanib (tyrosine kinase)				
Phase III/IV	• Ambrisentan (endothelin receptor)	• Obeticholic acid (FXR)	• Beraprost (prostacyclin)		• Statins (HMG-CoA reductase inhibitor)
	• Bosentan (endothelin receptor)	• Metadoxine (5HT)	• Atrasentan (endothelin receptor)		
		• Pioglitazone (PPARγ)	• Pirfenidone		
		• Losartan (ARB/RAAS)			
		• Statins (HMG-CoA reductase inhibitor)			
Phase II	• BMS-986020 (LPA)	• Simtuzumab (LOXL2)	• GKT137831 (NOX)	• Imatinib (tyrosine kinase)	• Pirfenidone
	• Iloprost (prostacyclin)	• Emricasan (caspase inhibitor)	• Pyridoxamine	• SAR100842 (LPA)	
	• Treprostinil (prostacyclin)	• Cenicriviroc (CCR2/CCR5)	• Baricitinib (JAK)	• Bosentan (endothelin receptor)	
	• BG00011 (αvβ6)	• GR-MD-02 (galectin)	• Bindarit (indazolic derivative)	• P144 (TGF-β1)	
	• Macitentan (endothelin receptor)	• GFT-505 (PPARα/δ)	• CTP-499 (PDE)	• Pomalidomide	
	• Lebrikizumab (IL-13)	• Hydronidone	• Fresolimumab (TGF-β1)	• Paquinimod (S100A9)	
	• Tralokinumab (IL-13)	• FG-3019 (CTGF)		• Pirfenidone	
	• QAX576 (IL-13)	• Pirfenidone		• Statins (HMG-CoA reductase inhibitor)	
	• Dasatinib (tyrosine kinase)				
	• FG-3019 (CTGF)				
	• PRM-151 (serum amyloid P)				

(continued)

Table 23.1 (continued)

	Lung	Liver	Kidney	Skin	Heart
Phase I	• GSK2126458 (mTOR)		• FG-3019 (CTGF)	• Treprostinil (prostacyclin)	
	• Sirolimus [pilot] (mTOR)			• Fresolimumab (TGF-β1)	
	• Fresolimumab (TGF-β1)				
	• Losartan [pilot] (ARB/RAAS)				

or pathway is included under the organ in which the most relevant or recent clinical trials are being performed, although many of these molecules will have supporting evidence for use in organs other than the one in whose section they appear.

23.2 Liver

The mechanisms of liver fibrosis are the subjects of intensive investigation, and multiple potential therapies targeting important pro-fibrotic pathways are under study [11, 12].

23.2.1 Farnesoid X Receptor (FXR)

The farnesoid X receptor (FXR) has been implicated as an important player in both inflammatory bowel disease [13] and hepatic inflammation and fibrosis [14–16]. 6-ethylchenodeoxycholic acid (obeticholic acid) is a synthetic bile acid that is an activator of the farnesoid X nuclear receptor [17]. The effect of lipophilic bile acid antagonism of FXR in NASH is thought to be secondary to effects on metabolism, insulin sensitivity, and decreases in circulating triglycerides as well as hepatic gluconeogenesis [17–19].

Recently, a multi-center, double-blind, placebo-controlled trial of (obeticholic acid) for patients with non-alcoholic steatohepatitis demonstrated histological benefit, including improvement in fibrosis [17]. Additionally, a phase 3 trial evaluating the long term benefit of obeticholic acid in patients with NASH fibrosis is currently recruiting (Randomized Global Phase 3 Study to Evaluate the Impact on NASH with Fibrosis of Obeticholic Acid Treatment; REGENERATE Trial. ClinicalTrials.gov NCT02548351).

The mechanism of the anti-fibrotic effect seen in NASH is thought to be primarily metabolic modulation, and may not have translation to intestinal disease. However FXR has been shown to be expressed in the small intestine as well as many other organs [15, 20–22]. Further, FXR is thought to be important in intes-

tinal barrier function as well as immune modulation [23], and FXR activation has demonstrated an anti-inflammatory effect in animal models of inflammatory bowel disease [13].

23.2.2 Lysyl Oxidase (LOXL2)

Lysyl oxidase (LOX) genes represent another potential target for anti-fibrotic therapy. One particular member of this family, lysyl oxidase like-2 (LOXL2), is thought to be a promising target for anti-fibrotic therapy due to its effects in cross-linking the extracellular matrix, and has been linked to fibroblast activation in cancer cells [11, 24]. LOXL2 has been shown to be increased in tissue from fibrotic lung and liver, and inhibition of LOXL2 in mouse cancer models demonstrated a reduction in activation of fibroblasts, decreases in growth factor and cytokine production, and a reduction in transforming growth factor-beta (TGF-β) [25]. LOXL2 has also been implicated as an important pathway in cardiac fibrosis related to heart failure, with increased levels in diseased human cardiac tissue and serum, and a reduction in fibrosis with gene knock-out and anti-LOXL2 antibody treated transaortic constriction mouse models of cardiac disease [26].

Simtuzumab is a humanized IgG4 monoclonal antibody that targets LOXL2. In a phase 2, open label study to assess safety, tolerability, and potential efficacy in liver fibrosis in HIV and/or HCV infected adults, Simtuzumab demonstrated safety and tolerability, but did not demonstrate improvement in fibrosis [27]. Additionally, a phase 2b, randomized, double-blind placebo-controlled trial of simtuzumab in patients with non-alcoholic steatohepatitis (ClinicalTrials.gov NCT01672866) was recently terminated. Simtuzumab has been investigated in the lung as well, but unfortunately failed to demonstrate efficacy in a clinical trial for idiopathic pulmonary fibrosis [28]. Despite this lack of efficacy of Simtuzumab in clinical trials, the promising data from in vitro and animal models combined with safety in human subjects maintains this pathway as worthy of further investigation.

23.2.3 Statins

Statins, or HMG-CoA reductase inhibitors, are actively being investigated as potential antifibrotic agents in liver disease. Traditionally used for their lipid-lowering effects, the potential of statins to impart clinical benefits beyond prevention of coronary and arterial vascular disease are increasingly being recognized and studied [11, 29, 30]. Statins are now thought to have anti-fibrotic, anti-inflammatory, antioxidant, and immunomodulatory effects. The multi-faceted impact of statins is due to their pleiotropic effects. These are a result of a reduction or down-regulation of isoprenoids, which are critical for the function of many GTPases. RhoA is one such GTPase, and a decrease in its activity has been proposed as a potential mechanism for the anti-fibrotic effects.

The anti-fibrotic effect of statins in liver disease has been demonstrated in in vitro and in vivo models of liver fibrosis [31–34]. Further, post hoc analysis of the results of the HALT-C (Hepatitis C Antiviral Long-Term Treatment against cirrhosis) trial have suggested that statin use could potentially reduce progression of fibrosis in chronic hepatitis C patients [35]. In addition to the liver, the anti-fibrotic potential of statins is also being investigated in the lung [36] and heart [37], and there are currently several clinical trials of statins for fibrosis at various stages of completion for fibrosis in several organs including the liver, skin, and heart.

Statins have also been investigated in intestinal fibrosis, and simvastatin has demonstrated anti-fibrotic potential in TNBS-induced colitis mouse model of fibrosis [38]. These encouraging results make statins a potential generic, low-cost, and effective anti-fibrotic therapy.

23.2.4 5-Hydroxytryptamine (5HT)

The serotonin signaling system is thought to be important in exerting both proliferative and anti-proliferative effects on parenchyma in the liver, and antagonism of the 5-hydroxytryptamine (5HT) receptor has been shown to enhance regeneration and reduce fibrosis in hepatocytes [39, 40]. Serotonin derived from platelets has been shown to stimulate extracellular matrix synthesis through 5-HT_{2B} receptors via a TGF-β dependent mechanism [41]. This study utilized dermal fibroblasts, transgenic mice, and a bleomycin-induced dermal fibrosis mouse model to demonstrate the importance of serotonin, primarily from platelets, in the development of experimental skin fibrosis. Further, the use of cyproheptadine and terguride as 5-HT_2 inhibitors in this study established them as potential anti-fibrotic therapies. Terguride has demonstrated anti-fibrotic activity in cardiac fibrosis in a pulmonary artery banding mouse model of right heart failure [42]. The importance of serotonin 5-HT_2 receptors, and the potential therapeutic effect of antagonism of those receptors, has also been demonstrated in a bleomycin-induced mouse model of pulmonary fibrosis [43].

Metadoxine has many pharmacological properties such as restoration of glutathione, NADH, and ATP levels [44]. Some of its effects are thought be related to serotonin 5-HT_{2B} antagonism. Metadoxine is currently approved for alcoholic hepatitis. Metadoxine has shown anti-fibrotic potential in hepatic stellate cells in culture [45], as well as murine models [46]. In humans, a randomized placebo-controlled trial of metadoxine vs. placebo in NASH demonstrated improvement in steatosis, but no difference in ALT, AST, or liver histology [44]. A phase III trial of Metadoxine as therapy for patients with NASH is currently underway (ClinicalTrials.gov NCT02541045). The established safety of Metadoxine and its potential anti-fibrotic effect make the investigation of this drug and others affecting 5HT signaling an intriguing avenue for investigation in liver fibrosis and intestinal fibrosis.

Platelets have been identified as an important source of serotonin in the lung, skin, in wound healing, and in hepatic regeneration and fibrosis [40, 41]. Elevated platelet count and elevated platelet:albumin ratio have been reported to be significant risk factors for surgery in stricturing small bowel Crohn's disease [47]. In addition to direct antagonism of serotonin signaling, anti-platelet therapy represents an intriguing potential anti-fibrotic therapy.

Clopidogrel, which exerts anti-platelet effects via antagonism of the adenosine diphosphate, G-protein coupled receptor $P2Y_{12}$ [48, 49], is currently widely used for the treatment of acute coronary syndrome, myocardial infarction, stroke, and peripheral arterial disease. Inhibition of platelet activation with clopidogrel was shown to be anti-fibrotic in an angiotensin II mouse model of cardiac inflammation and fibrosis [48].

Thus inhibition of the 5HT pathway, and inhibition of platelet activation, represents intriguing potential targets for anti-fibrotic therapies in the intestine.

23.2.5 Caspase Inhibition

Inhibition of caspases represents another potential avenue for anti-fibrotic therapy. Despite apoptosis being well described as less inflammatory compared to necrosis as an inducer. [50, 51] Fas-mediated apoptosis of hepatocytes has been shown to activate fibrogenesis in murine models [52]. Interference with Fas-mediated apoptosis has shown anti-fibrotic potential in bile duct ligation, concanavalin A, and Jo2 monoclonal antibody mouse models of hepatitis and liver fibrosis [52–54]. These findings have led investigators to pursue stellate cell apoptosis as a potential anti-fibrotic therapeutic target. Selecting death receptors specifically as therapeutic targets is complicated by the fact that they exert effects through a variety of intracellular cascades. One such cascade relies on caspases, which are key effectors of apoptosis [55, 56]. Despite the existence of at least 13 mammalian caspases, broad spectrum caspase inhibitors have been synthesized and demonstrated potency as anti-apoptotic agents [53, 57, 58]. One such inhibitor, Emricasan (IDN-6556), has demonstrated efficacy in reducing hepatic fibrosis in murine models [53, 59], and has entered clinical trials [60]. Currently Emricasan is being studied in a phase II clinical trial of patients with liver fibrosis and hepatitis C reinfection after liver transplant (ClinicalTrials.gov NCT02138253). This double-blind, randomized, multicenter trial is evaluating the effects of IDN-6556 versus placebo on liver fibrosis in these patients, and is expected to conclude in early 2018. While this apoptotic pathway is thought to target hepatocellular stellate cells as key mediators/effectors of fibrosis, it is plausible that similar induction of apoptosis in myofibroblasts in the intestine could produce therapeutic benefits in IBD. Furthermore, the ubiquity of caspases as downstream effectors of apoptosis presents a promising potential target that could be effective in multiple organ systems.

23.2.6 Chemokine Receptors CCR2/5

Monocytes and macrophages are recognized as being important mediators of liver fibrosis [61]. Chemokines are critical mediators of cell function and act through G-protein coupled chemokine receptors (CCRs) [62]. Chemokines are recognized as important mediators of inflammation and are also thought to play an important role in orchestrating fibrosis in liver disease [63], and the CCR phenotype profile of monocytes is likely an important determinant of function. The chemokine receptors CCR1, CCR2, and CCR5 are implicated as being pro-fibrotic in murine models of liver fibrosis [64–66]. CCR2 has also been linked to inflammation and fibrosis in the kidney [66–68] and lung. [66, 69, 70] Thus, CCRs represent an intriguing target for anti-fibrotic therapies in the liver and other organs.

Cenicriviroc is a small molecule inhibitor of both CCR2 and CCR5, and has demonstrated safety in early trials of human patients afflicted with HIV-1, [71–73] as well as a phase IIb trial (ClinicalTrials.gov NCT01338883) [74, 75]. Cenicriviroc has also demonstrated therapeutic potential in animal models of liver fibrosis as well as renal fibrosis [76]. A phase II trial of cenicriviroc in patients with NASH and liver fibrosis is planned to complete in late 2017 and (ClinicalTrials.gov NCT02217475). This trial, also called "CENTAUR: Efficacy and Safety Study of Cenicriviroc for the Treatment of Nonalcoholic Steatohepatitis (NASH) in Adult Subjects With Liver Fibrosis," is a double-blind, placebo-controlled, randomized multinational study with the primary endpoint being histologic improvement of NASH activity score without worsening of fibrosis in patients with NASH and liver fibrosis [77]. Results of this study are pending. An open label rollover extension study of participants in CENTAUR began in early 2017 and is ongoing (ClinicalTrials.gov NCT03059446).

There is evidence that CCRs are important in fibrosis in the liver, lung and kidney. At least one molecule that inhibits CCRs has demonstrable safety in human subjects. As such, blockade of CCRs with molecules such as Cenicriviroc represent another potential therapeutic avenue for the treatment of fibrotic inflammatory bowel disease.

23.2.7 GR-MD-02

Galectins are a family of proteins with a carbohydrate binding domain that may be influential in immune and inflammatory processes [78, 79]. One member of this family, galectin 3, is thought to be important in inflammation [80] and has shown to be an important regulator of fibrosis in experimental models of both the liver [81] and lung [82]. Inhibition of galectin-3 with a novel carbohydrate inhibitor, GR-MD-02, has been shown to reduce fibrosis and even reverse cirrhosis in animal models [83]. GR-MD-02 has demonstrated safety and tolerability in a phase 1 trial in patients with NASH [84]. There is a recently completed phase 2 trial of

GR-MD-02 in patients with NASH (NASH-FX) (ClinicalTrials.gov NCT02421094) and an additional phase 2 trial in patients with NASH and portal hypertension (NASH-CX) (ClinicalTrials.gov NCT02462967). Results have not been published for either, but it was announced that GR-MD-02 did not meet the primary endpoint of change in liver fibrosis measured by LiverMultiScan, nor did it meet secondary endpoints of change in liver stiffness measured by MR-elastography or stiffness measured by FibroScan®.

23.2.8 PPAR Gamma

Members of the nuclear receptor peroxisome proliferator-activated receptor (PPAR) nuclear receptor superfamily have an array of effects and are involved in metabolic processes, inflammation, and fibrosis [85, 86]. Thiazolidinediones are ligands for the nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR-γ) that are potent insulin sensitizers but have an array of effects related to modulation of gene expression [85]. Thiazolidinediones are widely used in the treatment of diabetes, and their potential for use as in liver fibrosis is an active area of investigation [11, 12].

Pioglitazone demonstrated an anti-fibrotic effect in a choline-deficient L-amino acid-defined diet rat model of liver fibrosis [87]. It was also shown to be anti-fibrotic in a bleomycin-induced rat model of lung fibrosis [88] The PIVENS trial was a phase III trial evaluating pioglitazone, vitamin E, or placebo in patients with NASH [89]. Pioglitazone failed to achieve significance in the primary outcome (a combination of histological findings, fibrosis and disease activity scores), but did improve steatosis, inflammation, hepatocellular ballooning, and liver enzyme levels [90]. In a proof of concept study in patients with type 2 diabetes or impaired glucose tolerance and NASH, pioglitazone improved liver enzymes, decreased hepatic fat content, and improved some histological findings but failed to significantly reduce fibrosis [91]. Interestingly, in a clinical trial in non-diabetic patients with NASH, pioglitazone did improve fibrosis assessed by histologic features [92].

Pioglitazone also is/has been evaluated in several clinical trials without complete results as of yet. These include a phase IV trial in patients with type 2 diabetes and NAFLD, which is complete but no results have been published (ClinicalTrials.gov NCT01002547); a separate phase IV trial of pioglitazone in patients with NAFLD and type 2 diabetes (UTHSCSA NASH Trial) is completed, (results are available on ClinicalTrials.gov but not analyzed) (ClinicalTrials.gov NCT00994682); and a phase II trial to evaluate long term safety and efficacy in NASH, (results are available on ClinicalTrials.gov but not analyzed) (ClinicalTrials.gov NCT00062764).

Rosiglitazone showed anti-fibrotic activity in a bleomycin-induced mouse model of scleroderma [93], and a bleomycin-induced rat model of pulmonary fibrosis [94]. Rosiglitazone has demonstrated some antisteatogenic efficacy in short but not long term therapy for patients with NASH in the FLIRT/FLIRT-2 trials, and there was no improvement in fibrosis in this trial [95, 96]. In a phase II clinical trial, a different

PPAR-γ agonist, farglitazar, failed to improve fibrosis in patients with chronic hepatitis C [97].

GFT-505 (elifibranor) is a dual agonist of PPAR-α and PPAR-δ being studied for its metabolic effects [98, 99] that demonstrated anti-fibrotic effects in three murine models of liver fibrosis, (western-diet fed human apolipoprotein E2 transgenic mice, methionine-and choline deficient-diet—fed db/db mice, and CCl_4-induced fibrosis rats) [100]. A phase IIb clinical trial of GFT-505 in patients with NASH demonstrated a resolution of NASH without worsening of fibrosis, albeit on a modified definition from the original primary outcome (which was not met) (ClinicalTrials.gov NCT01694849) [101].

PPAR-γ agonists have been identified as potential targets for the treatment of ulcerative colitis given their role in modulation of inflammation and the immune response [102]. In vitro studies of troglitazone and rosiglitazone (PPAR-γ agonists), in human intestinal primary myofibroblasts recently demonstrated anti-fibrotic effects such as reduction in procollagen1A1, fibronectin, and α-smooth muscle actin [103]. If these agents demonstrate consistent anti-fibrotic effects they warrant further investigation for the treatment of intestinal fibrosis, particularly in patients with comorbid metabolic disease.

23.3 Lung

The study of anti-fibrotics for pulmonary disease is a rich and active area of investigation, and pulmonary fibrosis boasts two FDA approved anti-fibrotic medications (pirfenidone and nintedanib).

23.3.1 Pirfenidone

Pirfenidone is a pyridine derivative that has demonstrated anti-fibrotic and anti-inflammatory effects, and is approved for the treatment of idiopathic pulmonary fibrosis [104]. The exact mechanism of action of pirfenidone is yet to be elucidated. In a bleomycin-induced hamster model of lung fibrosis, pirfenidone has been shown to decrease biochemical markers of lung toxicity [105], suppress bleomycin-induced expression of transforming growth factor-beta (TGF-β) and lung procollagen 1 and III [106, 107]. Pirfenidone has also been shown to reduce or attenuate TGF-β mediated profibrotic activity in human lung fibroblasts via suppression or attenuation of α-smooth muscle actin, procollagen, and collagen synthesis and via suppression of human lung fibroblast proliferation [108, 109].

The clinical efficacy of pirfenidone has been studied in four phase III placebo-controlled randomized clinical trials. The first published phase III studied randomized 275 patients and evaluated a primary endpoint of change in vital capacity at week 52 for pirfenidone vs placebo [110]. Pirfenidone demonstrated superiority in

both the primary endpoint ($p = 0.0416$), as well as secondary endpoint of progression free survival ($p = 0.0280$) [110]. The results of the CAPACITY studies were published in 2011 [111]. CAPACITY 004 included 435 patients and demonstrated significance in its primary end point of change in percentage predicted forced vital capacity at week 72 ($p = 0.001$) [111]. CAPACITY 006 included 344 patients and evaluated the same primary endpoint, but failed to show a significant improvement in the pirfenidone group ($p = 0.501$) [111]. A fourth trial, ASCEND, was published in 2014 that included 555 patients and evaluated a primary endpoint of change in percentage of the predicted forced vital capacity at 52 weeks [112]. in the ASCEND trial pirfenidone demonstrated a significant improvement in the primary endpoint ($p < 0.001$), and also had favorable results for several secondary end points such as relative risk of death or disease progression and change from baseline for 6-min walk distance. Further, an analysis of pooled data from the ASCEND and CAPACITY studies included 1247 patients and suggested efficacy of pirfenidone for percent decline in predicted forced vital capacity as well as progression free survival, 6-minute walk distance, and dyspnea at 1 year [113]. Results of an open label extension study of one of the CAPACITY trials, RECAP, have also been published [114]. This study evaluated 178 patients previously randomized to placebo, and reports similar efficacy for forced vital capacity and survival for patients with idiopathic pulmonary fibrosis.

Pirfenidone appears to be generally well tolerated. In a recent prospective, observational, post-marketing surveillance study of 1371 patients, the most common side effects were decreased appetite, photosensitivity, nausea and abdominal discomfort [115]. Safety has also been evaluated in a pooled analysis of the CAPACITY trials, ASCEND trial, and two ongoing open label studies (study 002 and RECAP) [116]. This included analysis of 1299 patients for up to 9.9 years, and concluded that pirfenidone is safe and well tolerated in long term treatment. Most adverse events were mild to moderate, and the most common adverse events were nausea, diarrhea, dyspepsia, vomiting, and rash.

Pirfenidone has also been studied as a potential anti-fibrotic in the liver, kidney, heart, and eye [117]. There are currently multiple clinical trials of pirfenidone at varying stages of completion for the treatment of fibrosis in several organs, including the liver, kidney, skin, and heart.

Pirfenidone has demonstrated anti-fibrotic activity in the CCl_4 and bile duct ligation rat models of liver fibrosis [118]. It has also been shown to have anti-fibrotic effects in patients with chronic hepatitis C in a phase II clinical trial [119]. A randomized, double-blind, placebo-controlled trial of pirfenidone for the treatment of diabetic nephropathy demonstrated improvement in the primary outcome of mean change in eGFR for a dose of 1200 mg/day ($p = 0.026$) but not 2400 mg/day [120]. Despite completion of a clinical trial for pirfenidone in hypertrophic cardiomyopathy (ClinicalTrials.gov NCT00011076), no results have been published.

A second pyridine derivative, hydronidone, has reportedly demonstrated some anti-fibrotic efficacy in rat and mouse models of liver fibrosis, (although these data have not been published), and was well tolerated in a small first-in-human study [121]. A phase II clinical trial of hydronidone in patients with liver fibrosis

secondary to hepatitis B chronic hepatitis is currently recruiting (ClinicalTrials.gov NCT02499562).

These data make pirfenidone and other pyridine derivatives exciting agents for investigation in intestinal fibrosis. However, extrapolating potential efficacy from one organ system to another is made more difficult by the lack of understanding of the mechanism of action. Further complicating the use of pirfenidone for intestinal fibrosis is the incidence of gastrointestinal side effects associated with its use. Despite that, the action on TGF-β signaling, which is also known to be important in fibrosis in many organs including the intestine, highlights pirfendone as a potential anti-fibrotic for a broader array of fibrotic disease.

23.3.2 Nintedanib/Tyrosine Kinase Inhibitors

Tyrosine kinase inhibitors are actively being studied as potential anti-fibrotics in several different organ systems. Nintedanib is an indolinone derivative that inhibits multiple tyrosine kinases including vascular endothelial growth factor receptors, fibroblast growth factor receptors, and platelet-derived growth factor receptors [122, 123]. It is approved for the treatment of idiopathic pulmonary fibrosis, with clinical efficacy established in one phase II trial [124] and two phase III trials (INPULSIS) [125]. The phase II clinical trial was placebo-controlled and randomized 432 patients, and assessed the annual rate of decline of forced vital capacity as the primary endpoint [124]. In this study, the highest dose of nintedanib (150 mg twice daily, reduced the rate of loss of forced vital capacity by 68.4% compared to placebo, but did not reach statistical significance ($P = 0.06$). This study was followed up by the INPULSIS-1 and INPULSIS-2 studies, which were identical randomized, placebo-controlled, double-blind, 52-week phase III trials evaluating the annual rate of decline of forced vital capacity as the primary endpoint [125]. Between the two studies, 1066 patients were randomized. Both studies demonstrated a reduction in rate of decline in forced vital capacity with $p < 0.001$. The most frequent adverse event was diarrhea.

Nintedanib has also shown anti-fibrotic potential in TGF-β activated mouse fibroblasts, LX2 cells, primary human hepatic stellate cells, and the CCl_4 induced mouse model of liver fibrosis [126].

While the efficacy of nintedanib in idiopathic pulmonary fibrosis alone makes this agent worth investigation in intestinal fibrosis, and evidence of anti-fibrotic potential in liver models of fibrosis further supports more investigation, the incidence of gastrointestinal side effects may limit its utility for this purpose, and there has even been one report of colitis associated with its use [127].

At least two other tyrosine kinase inhibitors are under investigation as therapies for fibrotic disease.

Imatinib is another tyrosine kinase inhibitor approved for multiple cancers that has been studied in clinical trials for both idiopathic pulmonary fibrosis [128] as well as diffuse cutaneous systemic sclerosis [129] and scleroderma associated skin

fibrosis [130]. When studied for idiopathic pulmonary fibrosis, a randomized, placebo-controlled clinical trial failed to show improvement in survival or lung function [128]. In a phase IIa open label study for diffuse systemic sclerosis imatinib showed improvement in skin thickness and morphology as well as forced vital capacity [129]. In phase II randomized double-blind study for use in scleroderma-associated skin fibrosis imatinib failed to show efficacy [130]. A phase II study of imatinib for fibrosis in systemic sclerosis has been completed, but no results have yet been published (ClinicalTrials.gov NCT00613171).

Dasatinib is a pan-Src kinase inhibitor [131] approved for Philadelphia chromosome positive leukemia that has shown anti-fibrotic effects in in vitro fibroblasts from systemic sclerosis patients and a bleomycin-induced dermal fibrosis mouse model [132]. Phase I and II trials of dasatinib for scleroderma pulmonary fibrosis have been completed with some results available but not published or analyzed. (ClinicalTrials.gov NCT00764309).

23.3.3 Lysophospholipids

The lysophospholipid lysophosphatidic acid (LPA) is a small lipid that exerts an array of effects via action on G-protein coupled receptors [133]. Recently, several lysophospholipids and their receptors, including LPA, have emerged as potential therapeutic targets for an array of conditions that includes fibrosis, inflammation, and autoimmune disease [134]. LPA signaling has been identified as a potentially important mediator of lung fibrosis [135] and LPA has also been shown to be elevated in systemic sclerosis [136]. LPA antagonism also demonstrated anti-fibrotic potential in a bleomycin induced mouse model of lung fibrosis and a mouse model of scleroderma [137, 138]. The LPA receptor antagonist BMS-986020 has been studied in phase II clinical trials for the treatment of idiopathic pulmonary fibrosis, with results pending (ClinicalTrials.gov NCT01766817). In systemic sclerosis, the LPA inhibitor SAR100842 has also been studied in a phase II clinical trial (ClinicalTrials.gov NCT01651143) and showed a reduction in skin thickness and evidence of target engagement [139]. In the intestine, LPA signaling has been implicated in inflammation and colorectal cancer [140], and the emergence of LPA antagonists as potential anti-fibrotics in other organs certainly represents a potential therapeutic avenue for intestinal fibrosis as well.

23.3.4 mTOR

The mTOR pathway (and an upstream signaling molecule phosphatidylinositol 3-kinase [PI3K]) is thought to be important in immune disease, cancer, and even insulin resistance [141, 142]. The mTOR pathway has also been implicated as having importance in the development of fibrosis in several organs, and inhibition of

this pathway has been described to be anti-fibrotic in the kidney, liver, and lung [143–148]. Two drugs with mechanisms involving mTOR inhibition are currently in clinical trials for the treatment of idiopathic pulmonary fibrosis. GSK2126458 is an orally bioavailable, potent inhibitor of PI3Kα and mTOR that has been shown to inhibit the PI3K pathway in idiopathic pulmonary fibrosis lung tissue, fibroblasts, and bronchoalveolar lavage cells [149, 150]. A phase I proof of mechanism study in idiopathic pulmonary fibrosis has been completed, with results pending (ClinicalTrials.gov NCT01725139). Sirolimus (rapamycin) is an immunosuppressant used in organ transplantation that inhibits the mTOR pathway [151]. Rapamycin has demonstrated anti-fibrotic potential in a unilateral ureteral obstruction rat model of kidney fibrosis [147] and a transgenic TGF-α overexpression mouse model of pulmonary fibrosis [143]. A double-blind, placebo-controlled pilot study of sirolimus in idiopathic pulmonary fibrosis patients is ongoing (ClinicalTrials.gov NCT01462006).

In the intestine, one small retrospective case review found that sirolimus may be an effective rescue therapy in pediatric patients with severe refractory IBD [152].

While the mTOR pathway is an attractive potential anti-fibrotic target for intestinal disease, there are some roadblocks to its utility for this purpose. Rapamycin frequently causes diarrhea that is potentially mediated by reduction in the Na+/H+ exchanger 3 in the intestine, [153] and mTOR gene disruption in mice was shown to cause epithelial cell defects and atrophy following irradiation injury [154]. mTOR inhibition is known to cause well described oral ulceration, also called mTOR inhibitor-associated stomatitis [155, 156]. Perhaps of greatest concern is that mTOR inhibition causes impairment of wound healing, including in the intestine, and impairs healing of anastomoses [157–163]. In case reports, sirolimus has been implicated as a cause of small bowel ulceration [164], and a cause of impaired wound healing after metatarsal resection due to an infected plantar ulcer in a patient with type I diabetes status post kidney and pancreas transplantation [165]. In another case report, sirolimus toxicity has even been implicated as a potential cause of colonic perforation after development of colitis and ulcerations from leukocytoclastic vasculitis [166]. These well described effects of mTOR inhibition raise significant concern when considering their use for fibrosis associated with inflammatory bowel disease.

More investigation may be warranted pending anti-fibrotic efficacy in clinical trials.

23.3.5 Prostacyclin

Prostacyclin is a prostaglandin known to be a vasodilator and inhibitor of platelet aggregation that is increasingly recognized as an important inflammatory mediator in a variety of disease states [167]. Several prostacyclin analogues are currently approved for the treatment of pulmonary arterial hypertension.

Two such agents, iloprost and treprostinil, are currently under investigation in clinical trials as potential anti-fibrotic therapies [12]. Iloprost has been shown to

improve survival and prevent fibrosis in a bleomycin-induced mouse model of pulmonary fibrosis [168]. Iloprost is also used to treat scleroderma and Raynaud's phenomenon, and has been shown to reduce connective tissue growth factor (a pro-fibrotic cytokine) in patients with scleroderma [169].A randomized, double-blind, phase II clinical trial of iloprost in patients with idiopathic pulmonary fibrosis and elevated pulmonary arterial pressure has been completed, but no results are readily available (ClinicalTrials.gov NCT00109681). Treprostinil has been shown to improve digital ulcers in patients with systemic sclerosis [170], and has been studied in a phase I clinical trial in patients with systemic sclerosis (ClinicalTrials.gov NCT00848939). A phase II trial of treprostinil in patients with pulmonary hypertension and idiopathic pulmonary fibrosis was underway but terminated (ClinicalTrials.gov NCT00703339).

A third prostacyclin, beraprost, was shown to reduce renal tubular damage and tubulointerstitial fibrosis in a rat unilateral ureteral obstruction rat model of chronic kidney failure [171]. A phase IIb/III study of beraprost in patients with chronic kidney disease has been completed (ClinicalTrials.gov NCT01090037), but thus far only study design and rationale have been published [172].

The prostaglandin misoprostol has been shown to have effects on gastric mucosal blood flow, cellular permeability and epithelial proliferation, and has demonstrated efficacy for the treatment of NSAID-induced gastric ulcers [173], but is not routinely used for this purpose. Misoprostol has been shown to decrease orocecal transit time in healthy volunteers [174], and in a 3 week randomized double-blind cross over study of nine patients with severe chronic constipation, misoprostol reduced colonic transit time ($P = 0.0005$), increased stool weight ($P = 0.001$), and increased number of stools ($P = 0.01$) [175]. In a small open label trial of misoprostol for chronic refractory constipation, misoprostol enhanced colonic motility (particularly the left colon), but it's use was limited by high rates of withdrawal due to abdominal discomfort [176]. In a larger prospective randomized double-blind trial of misoprostol for improving postoperative intestinal motility, rectal misoprostol did not improve motility and in fact increased nausea and analgesic need [177].

Little work has been done to elucidate the role prostacyclins may play in intestinal fibrosis, but the demonstrable anti-fibrotic potential in the lung, skin, and kidney should position prostacyclins as a viable target for investigation in fibrotic intestinal disease.

23.3.6 Integrin αvβ6

Integrins are cell surface receptors thought to be involved in multiple processes including cell adhesion and migration [178]. αvβ6 is an epithelial-expressed integrin that is thought to be important in tissue repair [179, 180],and may have fibrosis mediating effects through activation of latent TGF-β [181]. αvβ6 has been shown to be up-regulated in a bile duct ligation mouse model of biliary fibrosis [182]. It has additionally been identified as a potential target for the treatment of idiopathic

pulmonary fibrosis [183],and several selective monoclonal antibodies targeting αvβ6 have been generated [184].A humanized monoclonal antibody that targets αvβ6 known as BG00011 (formerly STX-100) has been studied in a phase II clinical trial for idiopathic pulmonary fibrosis, but results are not yet published (ClinicalTrials.gov NCT01371305).

23.3.7 Endothelin Receptor Antagonism

The endothelin receptors ET_A and ET_B are vasoconstrictive, G-protein coupled receptors that bind the peptide endothelin [185]. Endothelin has been shown to be upregulated by TGF-β1 [186], interleukin-1 [187], and TNF-α [188]. Several endothelin receptor antagonists are currently in clinical use for pulmonary arterial hypertension, and there is active investigation into their use as a potential therapy for chronic kidney disease [185, 189, 190]. Endothelin receptor antagonism is also recognized as a potential anti-fibrotic therapy in many organs including the kidney, lung, liver, skin, and heart [12, 185, 191, 192].

Endothelin and ET receptors have long been implicated as important in idiopathic pulmonary fibrosis [193], and have been shown to induce epithelial-mesenchymal transition and reciprocally increase TGF-β1 in alveolar cells [194]. Bosentan is an antagonist of ET_A and ET_B [195, 196]. Bosentan improved fibrosis in a bleomycin-induced rat model of pulmonary fibrosis [197]. Bosentan failed to demonstrate efficacy in clinical trials for the treatment of idiopathic pulmonary fibrosis (BUILD-1, BUILD-3) [198, 199]. Bosentan also failed to demonstrate efficacy in clinical trials for use in interstitial lung disease secondary to systemic sclerosis [200]. Ambrisentan, a selective ET_A antagonist approved for use in pulmonary arterial hypertension, was studied in a phase III randomized, double-blind, placebo-controlled trial (ARTEMIS-IPF) (ClinicalTrials.gov NCT00768300) but was terminated early due to lack of efficacy and risk for respiratory hospitalization and disease progression [201]. Macitentan is another endothelin receptor antagonist used in pulmonary arterial hypertension that showed promise in pre-clinical studies but failed to demonstrate efficacy in a phase II clinical trial for idiopathic pulmonary fibrosis (MUSIC) [202].

Ambrisentan did show anti-fibrotic effect via inhibition of hepatic stellate cell activation and procollagen-1 and TIMP-1 gene expression reduction in a mouse model of NASH [203]. Endothelin receptor antagonism also reduced liver fibrosis and improved portal hypertension in CCl_4 treated mice [204].

Atrasentan is an ET_A receptor antagonist that demonstrated efficacy in reducing residual albuminuria when added to renin-angiotensin system blockade in patients with diabetic nephropathy [205]. A phase III clinical trial of atrasentan in patients with diabetic nephropathy is currently recruiting (SONAR) (ClinicalTrials.gov NCT01858532).

Endothelin receptor antagonists have also been studied for use in dermal fibrosis. Bosentan reduced the number of new ulcers but not the healing of existing ulcers in

patients with systemic sclerosis [206]. A phase II study of bosentan in systemic sclerosis has been completed (ClinicalTrials.gov NCT00318175), but results have not been published.

Despite a general lack of anti-fibrotic efficacy in clinical trials, particularly for pulmonary fibrosis, the pre-clinical data and effects on chronic kidney disease make endothelin antagonism a target worth investigating for inflammatory bowel related fibrosis. A recent study of atrasentan in TNBS-induced mouse model of colitis demonstrated an improvement in the severity of colitis, evidenced by macroscopic and microscopic score reductions and abrogation of levels of IL-1β, keratinocyte chemoattractant, and MIP-2 [207]. These encouraging data indicate a need for further characterization of the role of endothelin in inflammatory bowel disease, related fibrosis, and the potential for endothelin antagonists to be used as anti-fibrotic therapies in the intestine.

23.3.8 Interleukin (IL)-13

IL-13 is a cytokine and inflammatory mediator that is primarily secreted by type 2 helper T cells that increases TGF-β_1 production through action on the IL-13Rα_2 receptor [208, 209]. In animal models, IL-13 has been shown to be an important mediator of bleomycin-induced pulmonary [210] and TNBS-induced intestinal fibrosis [208, 211].

Lebrikizumab is a humanized monoclonal antibody that blocks IL-13 that has been shown to improve lung function in adults with asthma [212] and is being studied in an ongoing clinical trial for the treatment of IPF (ClinicalTrials.gov NCT01872689). A separate human monoclonal antibody against IL-13, tralokinumab, has been studied in two clinical trials for IPF (ClinicalTrials.gov NCT02036580) (completed, results available but not analyzed), and (ClinicalTrials.gov NCT01629667) (terminated due to lack of efficacy). A trial of tralokinumab as add on therapy for the treatment of ulcerative colitis did not improve clinical response (ClinicalTrials.gov NCT01482884) [213], but also did not worsen inflammation in ulcerative colitis. QAX576, another antibody against IL-13, has been studied in two clinical trials for pulmonary fibrosis (either IPF or secondary to systemic sclerosis) that have been terminated (ClinicalTrials.gov NCT01266135, NCT00581997) and one that is complete without results (ClinicalTrials.gov NCT00532233), as well as two trials for fistulizing Crohn's disease (ClinicalTrials.gov NCT01355614) and perianal fistulas in Crohn's disease (ClinicalTrials.gov NCT01316601) that are complete without results.

23.3.9 Connective Tissue Growth Factor

Connective tissue growth factor (CTGF) is recognized as an important mediator of growth factor activity that is involved in TGF-β signaling, has many important contributions to fibrosis including the production of extracellular matrix, and is emerging as a potential anti-fibrotic target [11, 214–216]. CTGF has been shown to be important in liver fibrosis [11, 215, 217], and blockade of CTGF with the anti-CTGF human monoclonal antibody FG-3019 has demonstrated anti-fibrotic effects in animal models of pulmonary [218] and dermal [219] fibrosis. FG-3019 has was found to be well tolerated in early clinical trials for several fibrotic diseases [9], including IPF [220], and diabetes with microalbuminuria [221]. A phase I study of FG-3019 for patients with Type I or II diabetes and diabetic nephropathy has been completed but results are not published (ClinicalTrials.gov NCT00754143) and an additional trial in patients with type II diabetes and kidney disease on ACE inhibitor or ARB therapy was terminated due to suboptimal study design (ClinicalTrials.gov NCT00913393). A phase II trial of FG 3019 for liver fibrosis secondary to chronic hepatitis B infection and beginning therapy with entecavir was unfortunately terminated due to the effects of entecavir alone (ClinicalTrials.gov NCT01217632). FG-3019 is currently being investigated in phase II trials for patients with IPF (ClinicalTrials.gov NCT01890265) (ClinicalTrials.gov NCT01262001).

23.3.10 Serum Amyloid P

Serum amyloid P (SAP) is a pentraxin protein and acute phase reactant similar to C-reactive protein [222]. SAP has been demonstrated to inhibit fibroblast differentiation [223]. This effect has been demonstrated using the serum of patients with scleroderma and mixed connective tissue disease or rheumatoid arthritis [224], a mouse model of ischemia/reperfusion cardiomyopathy [225], murine dermal wounds [226], and in the alveolar fluid in humans with acute respiratory distress syndrome compared to controls [227]. SAP has shown anti-fibrotic potential in transgenic mouse [228] and bleomycin-induced rat and mouse models of pulmonary fibrosis [229], and a radiation-induced hamster model of oral mucositis [230]. The human recombinant form of SAP, PRM-151, was well tolerated in two phase I trials for pulmonary fibrosis, [231, 232] and is currently being studied in a phase II trial for IPF (ClinicalTrials.gov NCT02550873).

23.4 Kidney

23.4.1 Nicotinamide Adenine Dinucleotide Phosphate Oxidases (NOX)

The nicotinamide adenine dinucleotide phosphate (NADPH) oxidases (NOX) are a family of enzyme complexes that are present throughout our body which produce reactive oxygen species (ROS) [233]. The generation of ROS by NOX is thought to play a role in a variety of diseases and NOX is recognized as a potential therapeutic target for the treatment of fibrosis [11, 12, 233]. Activation of NOX and oxidative stress from ROS has been shown to be important in hepatic fibrosis [234–237], pulmonary fibrosis [238–240], and kidney fibrosis [241, 242].

GKT137831 is a small molecule inhibitor of Nox 1 and Nox 4 [243, 244] that has been studied in a recent clinical trial for diabetic nephropathy. Studies of GKT137831 in animal models of fibrosis in the lung, liver, and kidney have suggested that it has potential as an anti-fibrotic therapy. In murine models of liver fibrosis consisting of wild type mice or superoxide dismutase upregulation mutant mice treated with CCl_4 or bile duct ligation, GKT137831 demonstrated anti-fibrotic effects via inhibition of ROS production and decreased fibrogenic gene expression [243]. In a separate study evaluating a bile duct ligated mouse model of liver fibrosis, GKT137831 also demonstrated a reduction in ROS and fibrogenic gene expression [245]. GKT137831 demonstrated partial reversal of age-associated persistent lung fibrosis in mice [238]. The anti-fibrotic potential of GKT137831 has also been demonstrated in a murine model of diabetic nephropathy [242]. A different Nox1/4 inhibitor, GKT136901, also showed anti-fibrotic potential in a murine model of diabetic nephropathy [246].

The NOX pathway has emerged as a clear potential target for anti-fibrotic therapies in a variety of organs, and GKT137831 has been studied in the liver and lung as well as kidney. At this time the results of a phase II clinical trial of GKT137831 in patients with type 2 diabetes mellitus with diabetic nephropathy (ClinicalTrials.gov NCT02010242) are yet to be published.

Along these lines, N-acetylcysteine (NAC) is believed to have a variety of activities including scavenging of ROS [247, 248], and has been studied in a multitude of disease states including pulmonary fibrosis. Open label studies of NAC were initially convincing for use in idiopathic pulmonary fibrosis [249], and a double-blind, randomized, placebo-controlled trial of NAC added to prednisone and azathioprine for the treatment of idiopathic pulmonary fibrosis reported efficacy [250]. A subsequent placebo-controlled trial included the above regimen as well as a NAC monotherapy group, and did not show benefit [251]. Of note, the three drug regimen was discontinued after interim analysis showed increased mortality and adverse events when compared to placebo [249, 251]. Ultimately, the evidence does not support the use of NAC as an anti-fibrotic agent for idiopathic pulmonary fibrosis [249].

The ubiquity of the NOX pathway and universally damaging effects of ROS would suggest good translation of NOX inhibition from other fibrotic diseases to use in the intestine. However, in one study comparing wild type to NOX1 knockout

mice in a dextran sulfate sodium-induced model of colitis, NOX1 appeared to be pivotal in mucosal repair and epithelial restitution [252]. Ultimately, further investigation into the role of NOX and ROS in intestinal fibrosis is needed.

23.4.2 Pyridoxamine

Pyridoxamine is a metabolite of vitamin B_6 that inhibits protein modification from advanced glycation end products and advanced lipoxidation end products [253, 254]. Pyridoxamine produced a decrease in cross-linking of skin collagen as well as inhibition of renal disease progression in a streptozotocin-induced diabetic rat model [255]. In phase II studies in patients with diabetic nephropathy, pyridoxamine reduced urinary TGF-beta 1 and was generally well tolerated [256]. A phase IIb clinical trial of pyridoxamine (Pyridorin) in diabetic nephropathy has been completed, with results yet to be published (ClinicalTrials.gov NCT00734253).

Glycation inhibition represents a clear potential target for chronic kidney disease and subsequent fibrosis given the effect of diabetes on these diseases. The potential benefit of this mechanism for intestinal fibrosis is less clear. However, pyridoxamine did reduce collagen cross-linking in the skin of diabetic animals and showed efficacy in the progression of kidney disease, which argues for a systemic anti-fibrotic effect in animals with diabetes. Should clinical trials of pyridoxamine for kidney disease demonstrate efficacy, this mechanism would warrant a close look for intestinal fibrosis, especially in patients with diabetes and fibrotic intestinal disease.

23.4.3 Janus Kinase (JAK)1/2

Janus Kinases (JAK) are a family of protein tyrosine kinases that are involved in cytokine signaling and serve critical functions in both immunity and inflammation [257, 258]. JAK2 is activated in systemic sclerosis in a TGF-β dependent manner, and in a bleomycin-induced mouse model of dermal fibrosis and a TSK-1 mouse model of systemic sclerosis, inhibition with the JAK 2 inhibitor TG101209 was shown to be anti-fibrotic [259]. Baricitinib (INCB028050) is a potent and selective inhibitor of JAK1 and JAK2 that is orally bioavailable [260], and is currently being developed for use in rheumatoid arthritis. A clinical trial of baricitinib for patients with diabetic kidney disease has been completed, with no results published as yet (ClinicalTrials.gov NCT01683409). A different JAK1/2 inhibitor, ruxolitinib, is approved for use in myelofibrosis and polycythemia vera.

In the intestine, the study of JAK inhibitors for use in inflammatory bowel disease is well under way, with other inhibitors such as filgotinib and tofacitinib actively being studied for the treatment of inflammatory bowel disease [261]. Of note, the authors have tested tofacitinib in three in vitro models of intestinal fibrosis, without any evidence of anti-fibrotic efficacy (personal communication, PDRH). In

addition to evaluating for efficacy in remission and maintenance, the efficacy of JAK inhibition in other fibrotic diseases suggests these drugs should be assessed for anti-fibrotic effects as well.

23.4.4 Bindarit-CCL (MCP) Inhibitor

The importance of chemokines in liver fibrosis has been previously discussed in this chapter. Chemokines are also thought to play pivotal roles in fibrosis in the kidney, lung as well as skin [262]. Bindarit, an indazolic derivative, is thought to exert anti-inflammatory effects via inhibition of monocyte and endothelial cell production of CC chemokine (CCL2) /monocyte chemotactic protein (MCP)-1, CCL7/MCP3, and CCL8/MCP-2 [263]. Bindarit demonstrated anti-inflammatory and anti-fibrotic effects in a porcine model of renal artery stenosis, and this was thought to be primarily due to its effect on MCP-1 [264]. A phase II study of bindarit for the treatment of diabetic nephropathy has been completed but no results have been published (ClinicalTrials.gov NCT01109212).

23.4.5 Phosphodiesterase Inhibition

CTP-499 is a novel phosphodiesterase inhibitor believed to have anti-fibrotic, anti-inflammatory, and anti-oxidative properties [265–267]. The molecule is a deuterium-containing methylxanthine derivative that shares a structure with the primary metabolite of pentoxyfylline with the exception of key hydrogens being replaced by deuterium [265]. Given the similarity in structure to the primary metabolite of pentoxyfylline, CTP-499 may have a similar mechanism to pentoxyfylline, which is also considered a potential therapy for chronic kidney disease [265, 268]. It has demonstrated anti-fibrotic potential in a unilateral ureteral obstruction rat model of renal fibrosis [269]. CTP-499 was well tolerated in a phase I trial [267] and a subsequent phase Ib safety and tolerability trial in chronic kidney disease [265]. A phase II study in type 2 diabetic nephropathy patients has been completed and results are not yet published (ClinicalTrials.gov NCT01487109).

Pentoxyfylline has been studied in experimental colitis, and was shown to inhibit fibrosis in TNBS-induced colitis in rats [270]. Pentoxyfylline-vitamin E was shown to inhibit the TGF-β1 cascade in radiation-induced enteropathy [271]. These data support CTP-499 as a potential therapeutic molecule in the treatment of intestinal fibrosis.

23.5 Skin

23.5.1 TGFβ Targeted Therapies

P144 is a peptide derived from the ligand-binding portion of the type III receptor of TGF-β that binds TGF-β1 and inhibits its activity [272]. Topical P144 treatment of bleomycin-induced skin fibrosis in mice demonstrated decreased dermal fibrosis, suppression of connective tissue growth factor, SMAD2/3 phosphorylation, and alpha-smooth muscle fibroblast development [273]. In cardiac fibroblasts it has been shown to decrease type I collagen synthesis and also inhibit TGF-β1 signaling, as well as a reduce profibrotic gene and protein expression in the myocardium of a spontaneous hypertensive rat model of cardiac fibrosis [274]. In another spontaneous hypertensive rat model, P144 reduced renal fibrosis, and also inhibited NADPH oxidase expression and oxidative stress in the kidney [275]. P144 also demonstrated anti-fibrotic effects in the liver via decreased number of activated hepatic stellate cells in CCL_4 treated rats [272]. Phase II clinical trials of topical P144 for skin fibrosis in systemic sclerosis have been completed but there are no results published (ClinicalTrials.gov NCT00574613) (ClinicalTrials.gov NCT00781053).

Fresolimumab is a human monoclonal antibody targeting TGF-β that was found to be well tolerated in a phase I study in treatment resistant primary focal segmental glomerulosclerosis (FSGS) [276], and is currently being studied in a phase II trial for FSGS (ClinicalTrials.gov NCT01665391). Fresolimumab also inhibited gene expression in TGF-β-mediated genes and showed clinical improvement measured by the modified Rodnan skin score in a phase I trial for patients with systemic sclerosis [277], and a phase I study in patients with IPF has been completed but no results have been published (ClinicalTrials.gov NCT00125385). A separate TGF-β1 specific humanized monoclonal antibody (LY2382770) was recently evaluated in a clinical trial in patients with diabetic nephropathy who were on renin-angiotensin system inhibitor therapy, but unfortunately this failed to improve serum creatinine and was terminated early due to futility [278].

Interestingly, the use of P144 as a topical agent could be potentially translatable to the treatment of intestinal fibrosis. If this molecule has good topical efficacy but poor absorption in the gut, it could constitute a gut-targeted therapy for fibrotic intestinal disease without systemic effects. This line of thinking currently lacks any demonstrated evidence, but should P144 prove efficacious for the treatment of dermal fibrosis, may warrant further investigation.

23.5.2 Thalidomide/Pomalidomide

Thalidomide is a molecule with an array of activities that has been studied in a wide variety of diseases, but its use has been limited due to well-known significant teratogenic side effects [279, 280]. In a bleomycin-induced lung fibrosis mouse model, thalidomide has been shown to inhibit TGF-β1 expression, reduce TGF-β1 and IL-6, and inhibit expression of ERK1/2 and phospho-ERK1/2 [281]. Thalidomide also inhibited lipopolysaccharide induced tumor necrosis factor alpha (TNF-α) [282, 283]. In addition to TNF-α inhibition, thalidomide has been shown to decrease production of TGF-β1, IL-6, VEGF, Ang-1, and collagen synthesis in human lung fibroblasts [284]. Thalidomide reduced the expression of TGF-β1, IL-6, VEGF, Ang-1, Ang-2, and COL1A1 in addition to improving fibrosis on histological examination of bleomycin-induced lung fibrosis in mice [284]. Thalidomide has been studied in clinical trials for idiopathic pulmonary fibrosis, with the only published clinical trial results being for the treatment of cough in idiopathic pulmonary fibrosis in which it did improve cough and respiratory quality of life [285].

The desire to optimize the therapeutic benefit of thalidomide while minimizing side effects gave rise to lenalidomide and pomalidomide, both of which are both significantly more potent inhibitors of TNF-α than thalidomide [279]. Lenalidomide is approved for use in multiple myeloma, myelodysplastic syndrome, and mantle cell lymphoma while pomalidomide is approved for use in multiple myeloma. Pomalidomide has also been studied as an anti-fibrotic in dermal fibrosis. In bleomycin-induced and tight-skin mouse models of dermal fibrosis, pomalidomide decreased expression of PAI-1, CTGF, and COL1A1 [286]. In the same study pomalidomide was also shown to decrease myofibroblast count, hydroxyproline, and dermal thickness. Pomalidomide has been studied in clinical trials for patients with systemic sclerosis and interstitial lung disease (ClinicalTrials.gov NCT01559129), with results not yet published.

Given the universal importance of TGF-β in fibrotic disease, as well as the importance of TNF-α in inflammatory bowel disease, these therapies represent an intriguing potential mechanism for anti-fibrotic therapy in the intestine. Thalidomide and its analogues have been studied for use in inflammatory bowel disease, but there is a paucity of randomized controlled trials or quality support for its use at large, and more studies are needed [287]. Whether or not thalidomide or its analogues could exert specific anti-fibrotic effects in the intestine, or achieve a therapeutic benefit that outweighs their significant side effect profile, remains to be seen.

23.5.3 Paquinimod

Paquinimod (ABR-215757) is a quinolone-3-carboxamide that inhibits the calcium binding protein S100A9 and is thought to have immunomodulatory properties [288, 289]. S100A9 is believed to be important in the modulation of inflammatory and epithelial cells [290]. In the tight skin 1 mouse model, paquinimod reduced skin thickness and TGF-β responsive gene expression [289]. An open label phase II study of paquinimod to evaluate biomarkers and safety in patients with systemic sclerosis has been completed, (ClinicalTrials.gov NCT01487551), but results have not been published.

23.6 Heart

The underlying mechanisms of cardiac fibrosis share many processes already discussed, and the treatment of cardiac fibrosis, particularly related to heart failure and ischemic disease, is an active area of investigation [291, 292]. Many therapies including β-blockers, loop diuretics, endothelin inhibitors, sildenafil, relaxin, ivabradine, and TNF-α antagonists have been considered for their potential anti-fibrotic effect in the heart, but the renin-angiotensin-aldosterone system (RAAS) and TGF-β appear to be the most prominent potential targets [291–293].

23.6.1 Renin Angiotensin Aldosterone System (RAAS)

Inhibition of the RAAS with Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and mineralocorticoid receptor blockers have well known clinical benefits in heart disease but are being increasingly investigated for their anti-fibrotic potential. Therapies modulating the RAAS axis are discussed under the cardiac section given their prominent use in mainstream medicine for cardiovascular disease.

Angiotensin II and its receptor, angiotensin type I receptor (AT1), exert a complicated array of pro-fibrotic effects including activation of macrophages, ROS mediated collagen production, and cardiac fibroblast stimulation [3].

RAAS inhibition also has known renoprotective effects, and angiotensin II is recognized as an important mediator and potential target in renal fibrosis [294]. In the lung, a pilot study of losartan in patients with IPF showed stabilization of pulmonary function [295]. In a CCl_4 induced liver fibrosis model in rats, losartan demonstrated anti-fibrotic effects as well as a reduction in AT1, TGF-β, and alpha smooth muscle expression [296]. A retrospective study including 284 chronic hepatitis C patients showed that patients with hypertension taking angiotensin-blocking therapy had less fibrosis than hypertensive patients who did not [297]. The ARB losartan has been studied in a phase III trial for anti-fibrotic effects in NASH (FELINE) (ClinicalTrials.

gov NCT01051219) and a pilot study for patients with idiopathic pulmonary fibrosis has been completed (ClinicalTrials.gov NCT00879879) with results not yet published.

Both ACE inhibitors and ARBs have demonstrated anti-fibrotic effects on cardiac fibrosis in clinical trials that is separate from their anti-hypertensive effects, and the mineralocorticoid receptor antagonists spironolactone and eplerenone have also demonstrated anti-fibrotic effects in patients with conditions such as heart failure, metabolic syndrome, and LV diastolic dysfunction [292].

The potential for the use of these agents in intestinal fibrosis is supported by studies showing that the ACE inhibitor captopril improved macroscopic and histologic lesions and pro-fibrotic gene expression in a TNBS-induced colitis rat model [298], and losartan similarly decreased macroscopic and microscopic fibrosis scores and TGF-β1 concentration in the TNBS induced colitis rat model [299].

23.6.2 Transforming Growth Factor (TGF)-β

TGF-β is also thought to be critical in the development of cardiac fibrosis [291–293]. Pirfenidone and tranilast have also been proposed as potential anti-fibrotic therapies in cardiac disease due to their ability to inhibit TGF-β [292, 293]. Activin receptor-like kinase 5 (ALK5) is a downstream signaler of the TGF-β pathway [300, 301] Unfortunately, in animal models, inhibition of ALK5 with SM16 and inhibition of TGF-β directly with antibodies demonstrated increased mortality despite anti-fibrotic effects on cardiac fibrosis [292, 301, 302].

23.7 Conclusion

The ubiquity of fibrosis as the pathway leading to chronic organ failure presents challenges, but also opportunities for collaboration across fields. As more breakthroughs occur in a variety of organs and disease states, the potential for these benefits to translate across organs is exciting and attainable (Fig. 23.1, Table 23.1). When approaching the problem of intestinal fibrosis in inflammatory bowel disease, it is important to also consider therapies and mechanisms in other organs, as there is much to be learned and knowledge to be shared.

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