Emerging therapeutic targets for the treatment of hepatic fibrosis

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Fibrosis represents a response to chronic injury, aimed at maintaining organ integrity. Hepatic fibrosis is mainly related to chronic viral hepatitis B or C (HBV or HCV), alcoholic and nonalcoholic steatohepatitis (NASH), and biliary diseases. A deep understanding of the cellular and molecular mechanisms underlying liver fibrosis has enabled the development of ‘pathogenetic tailored’ therapeutic interventions. However, effective drugs to prevent or revert hepatic fibrosis are still lacking. In this review, we discuss the cellular populations and the molecular pathways involved in liver fibrogenesis as well as the novel approaches currently being tested in clinical trials.

Introduction

Fibrosis represents a response to chronic injury, aimed at maintaining organ integrity when extensive necrosis or apoptosis occurs. Hepatic fibrosis is mainly related to chronic HBV or HCV infection, alcoholic steatohepatitis, NASH, and biliary diseases [1].

As fibrosis progresses, cirrhosis occurs, which comprises the replacement of functional parenchyma by scar tissue accompanied by a disruption of the architectural and vascular structure. Clinical consequences of cirrhosis are liver failure, portal hypertension, and a high risk of developing hepatocellular carcinoma (HCC). Liver fibrosis is a significant health problem, with a worldwide mortality attributable to cirrhosis and primary liver cancer of around 1.5 million deaths per year [2].

Fibrosis is a process strictly linked to wound healing, and serves to prevent tissues from disassembly during chronic, nonresolving inflammation. Following resolution of the tissue insult, fibrosis reverses within a few weeks; therefore, it is considered a dynamic event rather than a static process [3]. Regression of fibrosis and cirrhosis has been described in patients with iron and copper overload, alcohol-induced liver injury, chronic HBV, HCV, and HDV, hemochromatosis, secondary biliary cirrhosis, NASH, and autoimmune hepatitis [4,5].

However, chronic damage is associated with a progressive decline in the reversibility potential, even after the elimination of the triggering cause. This could be the result of different factors, including the acquisition of an atypical extracellular matrix (ECM) composition with advanced vascular remodeling, the extensive crosslinking of ECM components that makes fibrinolysis difficult to occur, and the loss of cellular elements able to digest the scar tissue.

The major actors in the fibrogenetic process are the activated myofibroblasts that derive from hepatic stellate cells (HSCs) and portal fibroblasts, but other cellular types within the liver parenchyma take part in the fibrogenic pathway, including sinusoidal endothelial cells, Kupffer cells, hepatocytes, and cholangiocytes.

Despite an improved understanding of the pathogenetic mechanisms of liver fibrosis, effective anti-fibrotic drugs are lacking and only preventive measures aimed at resolving the underlying causative factors of liver degeneration (i.e., antiviral therapies for HCV and HBV or strategies for metabolic syndrome) are used to decrease the burden of hepatic fibrosis.

Key cellular players in liver fibrogenesis

Recent evidence indicates that myofibroblasts, macrophages, endothelial cells, and biliary progenitors are the key cellular players in driving liver fibrinogenesis [1,6]. Here, we describe the current...
knowledge of how the dysregulated function of these cells contributes to the pathogenesis of liver fibrosis. Myofibroblasts not only promote scar tissue production and maintain organ integrity, but also contribute to fibrosis regression by releasing ECM-degrading proteases, in a process called ‘stress relaxation’. During stress relaxation, myofibroblasts contract on the accumulated collagen matrix and start to release ECM-degrading proteases, mainly metalloproteinases (MMPs) [7]. The ECM comprises collagen, glycoproteins, proteoglycans, and glycosaminoglycans, and provides cells with positional information and with a mechanical scaffold for cellular differentiation, migration, proliferation, and fibrogenic activation or deactivation. ECM-derived peptides regulate angiogenesis, and growth factor and MMP production. These signals either lead to stress activation, with a consequent fibrogenic response, or stress relaxation, with a fibrolytic response [7].

Studies using rodent models have shown that, during regression of liver fibrosis, approximately 50% of myofibroblasts undergo programmed cell death, whereas the remainder escape apoptosis, downregulate fibrogenic genes, and acquire a phenotype similar to, but distinct from, quiescent HSCs in their ability to rapidly reactivate into myofibroblasts in response to fibrogenic stimuli. In addition, inactivation of HSCs is associated with the upregulation of antiapoptotic genes, which contribute to the survival of HSCs, as observed both in vitro and in vivo [8]. However, a dual effect in liver fibrosis has been described for HSCs-derived myofibroblasts, because their depletion is associated with attenuation of both fibrosis and acute and chronic liver damage, unveiling an unexpected role in amplifying hepatocellular liver damage [9].

A role for macrophages in regulating fibrogenesis has also been proposed [4]. During chronic injury, Kupffer cells drive fibrosis progression by simultaneous activation of HSCs and stimulation of the recruitment of bone marrow-derived immune cells via the release of the chemokines chemokine (C–C motif) ligand 2 and 3 (CCL2 and CCL) [4]. The recruitment of immature monocyte-derived Ly6Chigh macrophages is dependent on CCL2 secreted by Kupffer cells and HSCs [10,11]. In rodent models, deletion of Ly6Chigh macrophages inhibited the profibrogenic response in a model of carbon tetrachloride (CCL4)-induced fibrosis. Hence, immature Ly6ChighCD11b+F4/80+ macrophages and their CCL2-dependent accumulation are a central mechanism of fibrosis activation and progression [11]. By contrast, fibrolytic macrophages derive from circulating Ly6Cint-expressing monocytes and develop locally into Ly6Cint-expressing macrophages expressing M2 markers and high levels of fibrolytic MMPs [12].

Sinusoidal endothelial cells are also crucial regulators of both liver regeneration and fibrosis [13]. Regenerative actions of these cells are mediated by C-X-C chemokine receptor type 7 (CXCR7), whereas profibrotic signals are induced by fibroblast growth factor-1 (FGF1) and CXCR4, which activate HSCs [13]. Conversely, myofibroblasts activate sinusoidal endothelial cells by secreting angiogenic factors, such as vascular endothelial growth factor (VEGF) and angiopoietin-1 [14].

Finally, biliary progenitor cells have been implicated in liver fibrosis. In fact, activated cholangiocytes (biliary progenitor cells) undergo a so-called ‘ductular reaction’, characterized by the formation of nonfunctional bile ductular structures in pathologies characterized by biliary fibrosis that can lead to liver fibrosis, including primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), and secondary biliary fibrosis. Once activated, cholangiocytes recruit HSCs to proliferate and secrete ECM components, and, in turn, these cells, along with other inflammatory cells, produce paracrine molecules that promote biliary cell proliferation and viability [15].

### Molecular pathways in fibrogenesis

Several and often unrelated molecular structures and signaling pathways might have a role in liver fibrosis [16,17]. Here, we review emerging data showing how their dysregulated functioning can lead to this disease and how they could represent new targets for therapeutic intervention. These systems include the inflammasome, farnesoid X receptor (FXR), mammalian target of rapamycin (mTOR), platelet-derived growth factor receptor (PDGFR) system, Galectin-3, and transforming growth factor β (TGFβ)-integrin αVβ6 axes.

In the complex network of intracellular events that occur during stellate cell activation, the inflammasome represents an important signal transducer in inflammatory cells, especially in fatty liver disease [18]. The inflammasome is a cytoplasmic protein complex required for cell recognition of pathogen-associated molecular patterns (PAMPs), as well as signals released by local tissue damage [19]. The inflammasome comprises nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), interacting with apoptosis-associated speck-like protein-containing CARD (ASC) adaptor molecules, which in turn activate cellular proteases. Expression of inflammasome proteins has been found in hepatic stellate cells [19] and, during fibrosis, myofibroblasts have been shown to maintain an activated state via a chronically activated inflammasome. This leads to the continual synthesis of collagens and other ECM proteins that results in damage to the tissue or organ [19] (Fig. 1). Among the inflammasome sensory molecules, NLR family, pyrin domain-containing 3 (NLRP3) has been characterized as being responsible for the regulation of hepatic stellate cell activation [19].

Other transcriptional events contributing to HSCs activation include the Wnt/β-catenin, GATA binding protein 4 (GATA4), and hedgehog signaling pathways [20]. The nuclear receptor family, which includes FXR, peroxisome proliferator-activated receptors (PPAR), Rev-erbα and liver X receptor (LXR), vitamin D receptor (VDR), and retinoid receptors [20], has also been extensively studied. In particular, the FXR is a family of nuclear hormone receptors whose natural ligands are bile acids, which seem to downregulate the activation of HSCs [21]. In vivo and in vitro data suggest that FXR ligands upregulate small heterodimer partner (SHP) in HSCs, and markedly reduce collagen I levels, abolishing MMP2 production and inhibiting the expression of tissue inhibitor of metalloproteinase 1 (TIMP1). Accordingly, the endogenous ligand chenodeoxycholic acid (CDCA) showed a significant anti-fibrotic effect in animal models [22]. Obeticholic acid is currently being tested in Phase II–III trials in patients with nonalcoholic fatty liver disease (NAFLD) NAFLD, NASH, PBC, or PSC (NCT02308111, NCT01473524, NCT02177136, NCT02548351, and NCT01265998) (Table 1). Along this line of research, preclinical studies are being conducted at Intercept Pharmaceutical on the use of dual FXR/TGR5 agonist INT-767 for liver fibrosis. A novel fully synthetic, nonsteroidal, and potent FXR agonist, PX-102,
produced by Phenex Pharmaceuticals, has completed Phase I trials and is currently in a Phase IIa study in patients with NAFLD.

Autophagy can also promote HSCs activation by providing energy substrates via retinyl ester hydrolysis [23]. In addition, the G protein exchange factor, GIV/Girdin, a convergent point of intracellular pathways regulating fibrosis, such as phosphoinositide 3-kinase–Akt–Forkhead box protein O1 (PI3K–Akt–FoxO1), TGFβ-SMAD and cAMP–protein kinase A–phosphorylated-cAMP-responsive element-binding protein (cAMP–PKA–pCREB), has been suggested to be a key regulator of HSCs activation [24].

One of the most potent mitogenic pathways in HSCs is represented by β-PDGFR signaling [25]. The expression of PDGFRs in liver increases dramatically in HSCs following injury [25]. Upon PDGF binding to its receptors, activation of the Fas–mitogen-activated protein kinase (MAPK) pathway through the PI3K–AKT–PKB pathway and activation of PKC family members occur. Targeting PDGFR signaling using tyrosine kinase inhibitors, such as imatinib mesylate (Gleevec®) and sorafenib (Nexavar®), has been proven to be effective in preclinical models of liver fibrosis [26,27].

Of particular relevance in this context is also the demonstration that the mTOR inhibitor, rapamycin, inhibits progression of hepatic fibrosis in rat model [28], because treatment with this drug has been shown to delay time to progression of liver fibrosis in HCV-transplanted recipients [29]; in addition it seems to favor the clinical course of HCV infection through anti-HCV action [30]. It has been further demonstrated that pathways downstream of mTOR activation, including mTOR complex 1 (mTORC1) and p70S kinases, could be involved in hepatic fibrosis and could represent a suitable therapeutic target [31].

Other molecular targets have recently attracted much attention and specific modulators of some of them have already entered clinical studies. Galectin-3 (Gal3) is a multifunctional protein of an expanding family of β-galactoside-binding animal lectins, mainly produced by macrophages [32], whose central role in liver fibrosis has been recently recognized in several preclinical and human studies. Gal3 stimulates HSC proliferation by activating the extracellular signal-regulated kinase (ERK)1/2 signaling pathway, whereas the β-galactoside-binding inhibitor, thiodigalactoside, reduced these effects [32]. Moreover, Gal32/2 mice show reduced fibrogenic response with attenuated expression of α-smooth muscle actin (α-SMA) and procollagen α1 [32]. Gal3 binding protein could be a candidate-marker of HCV-related fibrosis on the basis of serum proteomics [32]. Liver fibrosis in
### TABLE 1
Clinical trials with reduction of liver fibrosis as an end point.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Sponsor/Collaborator</th>
<th>Disease</th>
<th>Phase</th>
<th>NCT identifier/Refs</th>
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<td><strong>PPARγ agonists</strong></td>
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<td>GlaxoSmithKline</td>
<td>HCV</td>
<td>II</td>
<td>NCT00244751/[56]</td>
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<td>Rosiglitazone</td>
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<td>NASH</td>
<td>II</td>
<td>NCT00492700</td>
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<td>Pioglitazone</td>
<td>University of Florida/The University of Texas at San Antonio</td>
<td>NASH; NAFLD; T2DM</td>
<td>IV</td>
<td>NCT00994682</td>
</tr>
<tr>
<td>Sarogluzitazar; pioglitazone</td>
<td>Command Hospital, India</td>
<td>Fatty Liver</td>
<td>III</td>
<td>NCT02265276</td>
</tr>
<tr>
<td>G262570; FG-3019; Simtuzumab</td>
<td>GlaxoSmithKline</td>
<td>HCV</td>
<td>II</td>
<td>NCT00244751</td>
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<td><strong>Angiotsinin antagonists</strong></td>
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<tr>
<td>Losartan</td>
<td>Hospital Clinic of Barcelona</td>
<td>HCV; liver fibrosis</td>
<td>IV</td>
<td>NCT0298714/[57]</td>
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<td>Candesartan</td>
<td>Newcastle University</td>
<td>NASH</td>
<td>III</td>
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<td>Irbesartan</td>
<td>Inserm-ANRS/Sanofi</td>
<td>HCV</td>
<td>III</td>
<td>NCT00265642</td>
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<td>Moexipril (ACE inhibitor)</td>
<td>Mayo Clinic/UCB Pharma</td>
<td>PBC</td>
<td>II</td>
<td>NCT00588302</td>
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<td><strong>Cytokines/cytokines inhibitors</strong></td>
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<td>Pirfenidone</td>
<td>University of Guadalajara</td>
<td>HCV</td>
<td>Pilot</td>
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<tr>
<td>INF-γ</td>
<td>Huntington Medical Research Institutes</td>
<td>HBV</td>
<td>II</td>
<td>[59]</td>
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<td>INF-γ1b</td>
<td>InterMune</td>
<td>Liver fibrosis; cirrhosis</td>
<td>II</td>
<td>NCT00043303</td>
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<td><strong>Biologics</strong></td>
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<td>Simtuzumab (anti-LOXL2)</td>
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<td>Liver fibrosis; HCV</td>
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<td>NCT01707472</td>
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<td>FG-3019; (anti-CTGF)</td>
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<td>HBV</td>
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<td>Mesenchymal stem cell (MSC) injection</td>
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<td>Autologous mesenchymal stem cell transplantation</td>
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<td>Liver cirrhosis</td>
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<td>Umbilical cord-MSC transplantation</td>
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<td>Liver cirrhosis; end-stage liver disease</td>
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<td><strong>Anticoagulants</strong></td>
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<td>Warfarin, ximelagatran</td>
<td>Imperial College London</td>
<td>Liver fibrosis</td>
<td>II</td>
<td>NCT00180674</td>
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<td><strong>Glucagon-like peptide-1 analog</strong></td>
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<td>Liraglutide</td>
<td>Sun Yat-Sen University</td>
<td>NAFLD</td>
<td>II</td>
<td>[60]</td>
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<tr>
<td>Exenatide</td>
<td>Ruhr University of Bochum</td>
<td>NAFLD</td>
<td>IV</td>
<td>NCT01208649</td>
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<td><strong>Gal3 inhibitor</strong></td>
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<td>Galectin Therapeutics</td>
<td>NAFLD</td>
<td>II</td>
<td>NCT02421094</td>
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<td><strong>FXR agonists</strong></td>
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<td>Intercept Pharmaceuticals</td>
<td>Liver cirrhosis, biliary</td>
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<td>NCT02308111</td>
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<td>National Institute of Diabetes and Digestive and Kidney Diseases</td>
<td>Intercept Pharmaceuticals</td>
<td>Liver cirrhosis, biliary</td>
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<td><strong>CB1 inverse agonists</strong></td>
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<td>Rimonabant (SR141716)</td>
<td>Sanofi</td>
<td>Fatty liver</td>
<td>III</td>
<td>NCT00577148; NCT00576667</td>
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</table>
Sprague-Dawley rats was markedly attenuated with the two galec- 
tin protein inhibitors, galactoarabinono-hammogalacturanon and
galactomannan, which also reduced portal and septal Gal3-posi- 
tive macrophages [32]. Based on promising preclinical data, two 
Gal3 inhibitors are currently being tested in humans as antifibrotic 
drugs. The Gal3 inhibitor, GR-MD-02 (Galectic Therapeutics) is 
currently being tested in a Phase II trial in patients with NASH and 
advanced fibrosis (NCT02421094).

With respect to biliary fibrosis, antagonists of the biliary pro-
genitor-specific integrin αvβ6, which functions as a receptor for 
frbronectin and tenasin-C, and as an activator of TGFβ1, as well as 
inhibitors of the Hedgehog pathway, have been extensively stud-
ied and are currently in clinical trials (Table 1) [33,34].

Ongoing clinical trials

The growing progress in our understanding of the molecular 
mechanisms and pathways of hepatic fibrosis has enabled 
researchers to identify several promising molecular targets for 
antifibrotic treatments. A summary of the clinical trials is provided 
in Table 1.

Several PPAR-γ agonists (i.e., glitazones) have recently been 
tested. However, faralglitazar was recently shown to have no effect 
on collagen expression in patients with chronic HCV and moder-
ate fibrosis [35]. Rosiglitazone, pioglitazone, and saroglitizar are 
currently in Phase II–IV trials in patients with NASH, NAFLD, or 
chronic HCV (NCT00492700, NCT00994682, NCT00742326, 
NCT00189163, and NCT02265276).

The renin–angiotensin system (RAS) is implicated in liver 
fibrogenesis and portal hypertension. Activated HSCs produce 
angiotensin II, which is crucial for the development of liver 
fibrosis [36]. Accordingly, the inhibition of RAS, via angiotensin 
II antagonists, such as losartan and olmesartan, attenuates liver 
fibrosis development in animals [36]. Administration of the AT1R 
antagonist, losartan in patients with chronic HCV reduced fibro-
sis progression and downregulated expression of fibrogenic genes 
[37]. Currently, irbesartan, losartan, and candesartan and the 
angiotensin-converting enzyme (ACE) inhibitor, moexipril, are 
listed on ClinicalTrials.gov for the screening of their antifibrotic 
effects in HCV, NAFLD, NASH, ALD, and PBC (NCT00265642, 
NCT01051219, NCT00930995, NCT01913470, NCT00990639, 
and NCT00588302).

Although the TGFβ pathway has a key part in the fibrotic 
process, the development of drugs targeting this pathway is still 
in its infancy. Only pirfenidone, an orally available pyridine 
derivative that inhibits TGFβ production, has been tested in a 
small study in HCV-related fibrosis, showing to improve in the 
long-term both liver inflammation and fibrosis [38]. Moreover, 
given the antagonizing effect of interferon (IFN)-γ on TGFβ, a 
randomized controlled study demonstrated that IFNγ improves 
fibrosis scores in patients with chronic HBV infection after 9 
months of treatment [39]. IFNγ has also been shown to exert 
inhibitory effects on HSC growth, and to reduce the expression 
of type I and IV collagen, fibronectin, and SMA [40]. IFNγ1b is 
currently in a Phase II study in patients with liver fibrosis and/or 
cirrhosis (NCT0043303).

Several clinical trials to evaluate the efficacy of simtuzumab (GS-
6624), a monoclonal antibody targeting Lysyl oxidase-like 2 
(LOXL2), in patients with fibrosis of the liver are ongoing 
(NCT01452308, NCT01707472, NCT01672866, and 
NCT01672853). LOXL2 is a lysyl oxidase gene that has a role in 
the biogenesis of connective tissue, because it catalyzes the forma-
tion of crosslinks in collagens and elastin [41].

The anticoagulants warfarin and ximelagatran are currently in 
a Phase II study aiming to demonstrate improvements in surrogate 
markers of liver fibrosis over a short period of anticoagulation 
(NCT00180674). Indeed, patients who are predisposed to throm-
oses also appear to be more likely to develop rapid liver fibrosis if 
they are infected with HCV.

The Glucagon-like peptide-1 analogs, liraglutide and exenatide, 
are also being tested in patients with liver fibrosis (NCT01208649, 
NCT00650546). Liraglutide has already been shown to improve 
liver fibrosis markers in obese women with polycystic ovary syn-
drome and NAFLD [42].

Endogenous opioids have been shown to exert profibrogenic 
activity [43] and opioid antagonism has been tested in animal 
models [44]. Antagonism of the cannabinoid receptor CB1 in an 
acute model of injury resulting from CCH4 or in isolated cells 
leads to reduced cellular proliferation, increased myofibroblast apol-
tosis, and decreased expression of TGFβ [45]. By contrast, the CB2 
pathway is antifibrotic [46] and the CB2 receptor-selective agonist 
3-(1,1-dimethylbutyl)-1-deoxy-delta(8)-tetrahydrocannabinol 
(JWH-133) was found to decrease fibrosis in cirrhotic rats. The 
inverse agonist rimonabant (Sanofi) is currently in two Phase III 
trials (NCT00577148, NCT00576667).

Connective tissue growth factor (CTGF) is a secreted matricel-
lar protein that has been shown to regulate cell adhesion and mi-
gration, angiogenesis, myofibroblast activation, and ECM de-
position, leading to tissue remodeling and fibrosis. A monoclonal 
antibody to CTGF (FG-3019) is currently in clinical development 
for the treatment of liver fibrosis resulting from HBV infection 
(NCT01217632) [47].

Finally, the possibility of using stem cells to treat liver dis-
eases has been extensively explored in preclinical and clinical 
studies, with encouraging results [48,49]. At present, five Phase 
II trials using mesenchymal stem cells in patients with liver 
cirrhosis are listed on ClinicalTrials.gov under the identifiers: 
NCT01741090, NCT00476060, NCT01728728, NCT01877559, 
and NCT01854125.

Drugs tested in other fibrotic diseases

Fibrotic diseases include a range of clinical entities, both systemic, 
such as systemic sclerosis (SSc), scleroderma-tous graft versus host 
disease, and nephrogenic systemic fibrosis, and organ specific, 
such as pulmonary, liver, and kidney fibrosis [50]. Although 
fibrotic diseases are heterogeneous in their clinical manifesta-
tions, they share some common cellular and molecular pathways. 
This makes it reasonable to hypothesize that pharmacological 
strategies to treat one of these diseases would apply to other fibrotic 
diseases, including liver fibrosis.

As discussed above, blocking the TGFβ signaling pathway is a 
possible approach. However, in a Phase I/II trial, the human anti-
TGFβ1 monoclonal antibody, CAT-192, in patients with SSc 
showed no improvement in skin involvement or lung function 
parameters [51]. Pirfenidone has recently gained approval in dif-
ferent countries, including in Europe, USA, Japan, and China, 
for the treatment of idiopathic pulmonary fibrosis (IPF) [52].
Encouraging results come from a Phase I trial using the high-affinity neutralizing antibody that targets all three TGFβ isoforms; fostamabizumab resulted in decreased biomarkers levels and improved clinical symptoms in patients with SSc [53].

Integrins can activate matrix-bound TGFβ, and antibodies to integrin αvβ6 are able to block the activation of TG-β. A trial (NCT01371305) is currently recruiting patients with IPF to evaluate the safety and tolerability of subcutaneously administered multiple, escalating doses of the anti-αvβ6 mAb, STX-100, and to assess the effect of STX-100 on biomarkers isolated from bronchoalveolar lavage (BAL) and peripheral blood.

The adaptive immune system contributes to fibrosis via T helper type 2 (Th2) responses, which are characterized by the production of interleukin 4 and 13 (IL4 and IL13), which are potent inducers of fibroblast proliferation and collagen production [54]. The fully humanized monoclonal antibody against human IL13, QAX576, has been tested in two Phase II trials on IPF (NCT00532233, NCT01266135) and in one trial on pulmonary fibrosis secondary to SSc (NCT00581997). In addition, the tetravalent bispecific antibody against IL4 and IL13, SAR156597, is currently being evaluated for the treatment of IPF (NCT01529853, NCT02345070).

Imatinib mesylate is a small molecule that inhibits several tyrosine kinases, including c-AbI, PDGFR, and c-kit, by blocking the binding of ATP to the active kinase site. Encouraging results have been reported in clinical studies on patients with severe SSc [55], although imatinib exerted few beneficial effects on survival or lung function improvement in patients with IPF [56]. The novel tyrosine inhibitor BIBF 1120 has recently been approved in Europe for the treatment of IPF [52].

Endothelin-1 (ET-1) is a 21-amino acid polypeptide with potent vasoconstrictor activity that has been shown to stimulate the synthesis of types I and III collagen and to inhibit the production of matrix-degrading MMP1 in cultured normal human fibroblasts [57]. Bosentan, an endothelin receptor antagonist used in the treatment of pulmonary artery hypertension, has been approved in the European Union for reducing the number of digital ulcers in patients with SSc.

The Janus kinases (JAKs) are receptor-associated tyrosine kinases transducing cytokine and growth factor signaling. The JAK1/2 inhibitor ruxolitinib (Jakaft) is currently approved by the US Food and Drug Administration (FDA) for the treatment of patients with myelofibrosis [58]. A selective inhibitor of Gal3, TD139 (Galecto Biotech AB), is currently in a Phase I–II trial assessing its safety, tolerability, pharmacokinetics, and pharmacodynamics in patients with IPF [59]. Another Gal3 inhibitor from La Jolla Pharmaceutical (GCS100) had generated clinical proof of concept in Phase II studies in patients with chronic kidney disease (CKD) [http://www.businesswire.com/news/home/20141112006805/en/Results-Phase-2-Study-GCS-100-Chronic-Kidney#.Vg1B95fK-ZU].

Serum amyloid P or pentraxin 2 (PTX2) is a soluble pattern recognition receptor of the innate immune system that has been shown to inhibit the differentiation of circulating monocytes into fibrocytes and profibrotic macrophages [60]. PRM-151, a recombinant human PTX2 (Bristol-Myers) is currently under development for the treatment of IPF (NCT01254409, NCT02550873) and myelofibrosis (NCT01981850) [59].

**Concluding remarks**

The abrogation of the underlying causes of liver disease represents so far the most effective way to prevent fibrosis. This includes the removal of iron or copper excess in hemochromatosis or Wilson’s disease, the antiviral treatment of chronic HBV and HCV, the removal of bile duct obstruction, and abstinence from alcohol consumption. However, the emerging understanding of the cellular and molecular mechanisms underlying liver fibrosis is enabling the generation of new compounds that specifically target the dysregulated molecular pathways of the process. Moreover, emerging validated noninvasive biomarkers to monitor the fibrogenic and/or fibrolytic process of the liver and the definition of the optimal end points for antifibrotic trials could further optimize the clinical development of drugs for liver fibrosis.

Antifibrotic therapies should also be customized on the basis of disease-specific features and patient genetic characteristics, and multidrug approaches targeting mechanistically distinct components of the fibrogenic pathway could be pursued with the aim of having fewer and less toxic adverse effects. The possibility of delaying or halting the progression of fibrosis will be particularly important for those patients for whom disease-specific treatment is either not available or ineffective to preserve liver function, reducing the complications of cirrhosis and delaying the need for liver transplantation.

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