

# The scientific basis for novel treatments of systemic sclerosis

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## Abstract

In recent years, many potential antifibrotic treatment strategies have emerged from molecular studies of systemic sclerosis. Few biologicals have already entered clinical trials and these may hopefully prove to be effective in this progressive, profibrotic disease.

## Introduction and context

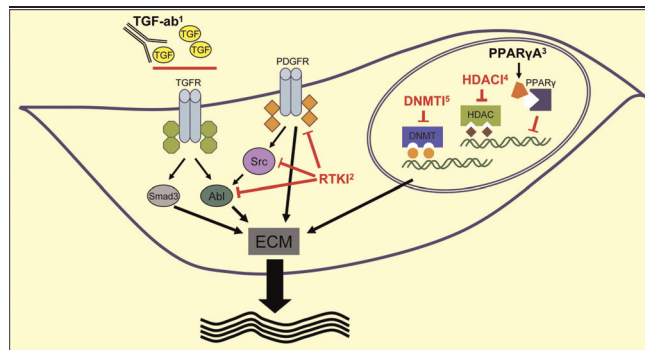
Vasculopathy, autoimmunity, and fibrosis are hallmarks of systemic sclerosis (SSc), a profibrotic disease that affects the skin and multiple internal organs, including the lungs, kidneys, gut, and heart [1]. In the late stages of SSc, progressive tissue fibrosis and organ failure cause high morbidity and increased mortality. Therapeutic options to treat patients with SSc symptomatically are limited, and causal therapies do not exist. In recent years, however, researchers have identified several key profibrotic molecules in the pathogenesis of SSc and have developed antifibrotic therapies, which now can be evaluated in clinical studies. Findings in preclinical models of SSc raised hopes that these antifibrotic therapeutics might restrain tissue fibrosis and alleviate patients' symptoms. Because of their mode of action, however, the antifibrotic therapies cannot target vasculopathy and autoimmune disease in patients with SSc. To develop causal treatment strategies, we still need to learn more about the pathogenesis of SSc.

## Recent advances

Both *in vitro* and *in vivo* studies indicate the central role of transforming growth factor-beta (TGF- $\beta$ ) in the development of fibrosis in SSc. TGF- $\beta$  stimulates fibroblasts to produce excessive amounts of extracellular matrix proteins, the predominant components of fibrotic tissue. Thus, inhibition of TGF- $\beta$  signaling can reduce tissue fibrosis in experimental models of SSc [2]. Nevertheless, recombinant TGF- $\beta_1$ -neutralizing antibodies (CAT-192)

failed to show efficacy in the first multi-center randomized placebo-controlled phase I/II trial [3]. Insufficient affinity to TGF- $\beta_1$  *in vivo* might explain treatment failure with the CAT-192 antibodies (Figure 1).

Imatinib interferes with two important profibrotic pathways in SSc as it inhibits the TGF- $\beta$  downstream kinase c-Abl and the tyrosine kinase activity of platelet-derived growth factor (PDGF) receptors [4]. In a murine model of radiation-induced pulmonary injury, imatinib inhibited the development of lung fibrosis [5]. In several experimental models of SSc, we demonstrated that imatinib prevented the development of fibrosis and reduced established skin fibrosis, suggesting its efficacy in both early and late stages of the disease [6,7]. Of note, smaller clinical studies in patients with chronic myelogenous leukemia (CML), in which imatinib is a first-line therapy, demonstrated regression of bone marrow fibrosis [8,9]. In addition, the first case reports indicated that imatinib mesylate could reduce established fibrosis in patients with SSc, mixed connective tissue disease, and nephrogenic fibrosis [10-12]. As shown by two recent studies, imatinib is highly effective in patients with refractory chronic graft-versus-host disease, which shares several pathologic features with SSc, including progressive skin fibrosis [13,14]. The antifibrotic effects in experimental models of SSc, its efficacy in other profibrotic disorders, and the large clinical experience from the treatment of CML prompted clinical trials currently evaluating the efficacy of imatinib in patients with SSc.

**Figure 1. Novel antifibrotic therapies in systemic sclerosis (SSc)**

Excessive accumulation of extracellular matrix (ECM) causes severe tissue fibrosis in SSc. Antifibrotic therapies target profibrotic pathways in fibroblasts, the main producers of ECM. <sup>1</sup>CAT-192 anti-transforming growth factor- $\beta$  antibodies (TGF-ab) catch TGF- $\beta$  molecules (TGF), which would bind to TGF- $\beta$  receptors (TGF $\beta$ R) to activate potent profibrotic pathways. Smad molecules, including Smad 3, as well as the Abelson kinase (Abl) are downstream mediators of the profibrotic TGF- $\beta$  pathway. <sup>2</sup>Receptor tyrosine kinase inhibitors (RTKI) can block several profibrotic signaling cascades. Imatinib and nilotinib inhibit both Abl and the platelet-derived growth factor receptor (PDGFR). In addition to Abl and PDGFR, dasatinib blocks Src kinases (Src). <sup>3</sup>The thiazolidinediones, a group of peroxisome proliferator-activated receptor- $\gamma$  agonists (PPAR $\gamma$ ), bind to their intra-nuclear receptors to inhibit ECM production. <sup>4</sup>Histone deacetylase inhibitors (HDACi) as well as <sup>5</sup>DNA methyltransferase inhibitors (DNMTi) decrease ECM production by modifying gene transcription.

Dasatinib and nilotinib, two novel inhibitors of c-Abl and the PDGF receptor, serve as salvage therapies for the treatment of refractory CML and in patients with intolerance to imatinib [15]. Similar to imatinib, dasatinib and nilotinib inhibited the development of fibrosis in *in vitro* and *in vivo* models of SSc and therefore might be interesting alternatives in the antifibrotic treatment with tyrosine kinase inhibitors. In addition to its direct effects on c-Abl and the PDGF receptor, dasatinib inhibits Src kinases. These enzymes regulate the activation of c-Abl and are activated by profibrotic cytokines, such as TGF- $\beta$  and PDGF. In experimental models of SSc, the specific inhibitor of Src kinase, SU6656, reduced the development of dermal fibrosis. Thus, targeting of Src kinases may be another promising approach in the treatment of SSc [16].

Peroxisome proliferator-activated receptor- $\gamma$  (PPAR- $\gamma$ ) is a member of the nuclear hormone receptor superfamily, which can activate a number of biological effects, including alterations in metabolic and inflammatory responses. The thiazolidinediones, a group of clinically approved PPAR- $\gamma$  agonists, lower blood glucose levels in patients with type 2 diabetes. PPAR- $\gamma$  agonists also suppressed cell activation and collagen

production in skin and lung fibroblasts and inhibited the development of fibrosis in murine models [17-19].

As targeted therapies in patients with malignancies, histone deacetylase (HDAC) inhibitors induce cell cycle arrest, cell differentiation, and apoptotic cell death of tumor cells [20]. Besides the cytotoxic effects on tumor cells, HDAC inhibitors can reduce the development of TGF- $\beta$ - and PDGF-induced fibrosis in experimental models of SSc. The non-selective inhibitor trichostatin A (TSA) inhibited TGF- $\beta$  signaling by preventing the nuclear translocation and the DNA binding of Smad3/Smad4 complexes in dermal fibroblasts. Upregulation of the cell cycle inhibitor p21 upon treatment with TSA may also reduce activation of fibroblasts and excessive production of extracellular matrix components [21]. Since the first clinical trials in patients with malignancies reported low toxicity, the antifibrotic effects in the preclinical models encourage clinical trials with TSA in SSc patients. Selective HDAC inhibitors (e.g., against HDAC-7) might offer even higher efficacy and lower toxicity [22].

Similar to HDACs, DNA methyltransferases (DNMTs) regulate DNA transcription by modifying the accessibility of genes to the transcription machinery. *In vitro* experiments demonstrated that the DNMT inhibitor 5-Aza-2-deoxycytidine decreased the release of collagen by restoring the transcription of *Fli-1*, which is hypermethylated and thereby silenced in SSc fibroblasts [23]. Furthermore, we showed that 5-Aza-2-deoxycytidine and other inhibitors of DNMTs, including procainamide and hydralazine, prevented the development of fibrosis in *in vivo* models of SSc [24].

### Implications for clinical practice

The thorough work of many researchers in our field has led to a better understanding of profibrotic pathways, the identification of target molecules, and the development of new therapeutic strategies in SSc. The tyrosine kinase inhibitor imatinib is currently under clinical evaluation for the treatment of patients with SSc and we are awaiting critical data from these trials. In contrast, the failure of the TGF- $\beta$ <sub>1</sub>-neutralizing CAT-192 antibodies *in vivo* requires further investigation. Since the pathogenesis of SSc remains enigmatic, we still face a lot of work to develop causal therapies for the treatment of SSc.

### Abbreviations

CML, chronic myelogenous leukemia; DNMT, DNA methyltransferase; HDAC, histone deacetylase; PDGF, platelet-derived growth factor; PPAR- $\gamma$ , peroxisome proliferator-activated receptor- $\gamma$ ; SSc, systemic sclerosis; TGF- $\beta$ , transforming growth factor-beta; TSA, trichostatin A.

## Competing interests

JHWD is involved in a clinical trial of imatinib in SSc that is sponsored by Novartis International AG (Basel, Switzerland). In addition, JHWD received grants from the Deutsche Forschungsgesellschaft (German Research Foundation), Interdisciplinary Center for Clinical Research in Erlangen, the Wilhelm Sander Foundation, and the Ernst Jung Foundation Career Support Award. JHWD has scientific cooperation with Novartis Pharmaceuticals, Array BioPharma (Boulder, CO, USA), Bayer Schering Pharma AG (Berlin-Wedding, Germany), Bristol-Myers Squibb (New York, NY, USA), Celgene Corporation (Summit, NJ, USA), and ErgoNex Pharma GmbH (Appenzell, Switzerland). JHWD received speaker fees from Actelion Pharmaceuticals Ltd (Allschwil, Switzerland), Encysive Pharmaceuticals (now part of Pfizer, Inc., New York, NY, USA), and GlaxoSmith-Kline (Brentford, Middlesex, UK). CB declares that he has no competing interests.

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