

 SYSTEMIC SCLEROSIS

Antiviral drug inhibits lung fibrosis

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Nelfinavir mesylate inhibited the development of lung fibrosis in an animal model of SSc



Nelfinavir mesylate, an antiretroviral drug used for the treatment of HIV, could be a potential new therapy for the treatment of systemic sclerosis (SSc) according to new findings published in *Arthritis & Rheumatology*. Nelfinavir mesylate inhibited the development of lung fibrosis in an animal model of SSc.

New therapies for SSc that have a lower toxicity and higher efficacy than currently used drugs are needed for treating pulmonary fibrosis. Nelfinavir mesylate is a safe approved drug for treating HIV. To investigate whether this drug can be repurposed for the treatment of SSc,

Sanchez *et al.* tested its effects *in vitro* on fibroblasts from both

healthy individuals and patients with SSc. Nelfinavir mesylate inhibited transforming growth factor β 1 (TGF β 1)-mediated myofibroblast differentiation of lung, skin and ventricular fibroblasts in a dose-dependent manner, as demonstrated by a reduction in the expression of collagen, fibronectin and α -smooth muscle actin. Treatment with this drug also increased autophagic degradation of type I collagen by differentiating fibroblasts, resulting in reduced myofibroblast contractility.

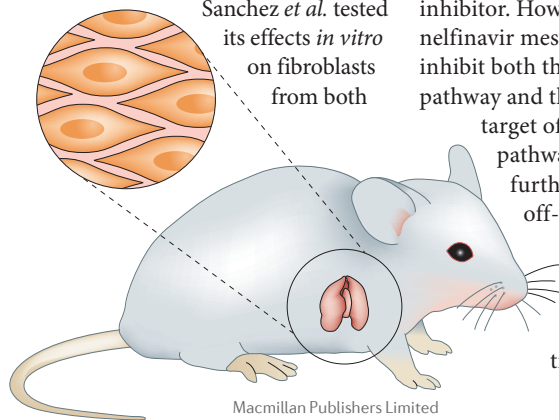
Mechanistically, nelfinavir mesylate inhibits HIV replication via its function as a protease inhibitor. However, in this study, nelfinavir mesylate was shown to inhibit both the canonical TGF β 1 pathway and the mechanistic target of rapamycin (mTOR) pathway in fibroblasts. To further investigate the off-target effects of this drug, Sanchez *et al.* used *in silico* proteome-wide screening to identify such interactions.

TGF β receptor 1 was identified as a top-scoring predicted target of nelfinavir mesylate, with results suggesting that nelfinavir mesylate has an inhibitory action on this receptor.

In a bleomycin-induced animal model of SSc, pretreatment with nelfinavir mesylate inhibited the development of lung fibrosis. Compared with vehicle treatment, mice exposed to nelfinavir mesylate had fewer lesions, a reduced amount of collagen deposition and reduced expression of connective tissue growth factor in the lungs.

These results highlight the therapeutic potential of nelfinavir mesylate for lung fibrosis due to its off-target inhibitory effects on fibrogenic pathways. The investigators propose taking this drug forwards for testing in patients with SSc in clinical trials.

Jessica McHugh



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ORIGINAL ARTICLE Sanchez, C. G. *et al.*
The antiretroviral nelfinavir mesylate, a potential therapy for systemic scleroderma. *Arthritis Rheumatol.* <http://dx.doi.org/10.1002/art.40326> (2017)