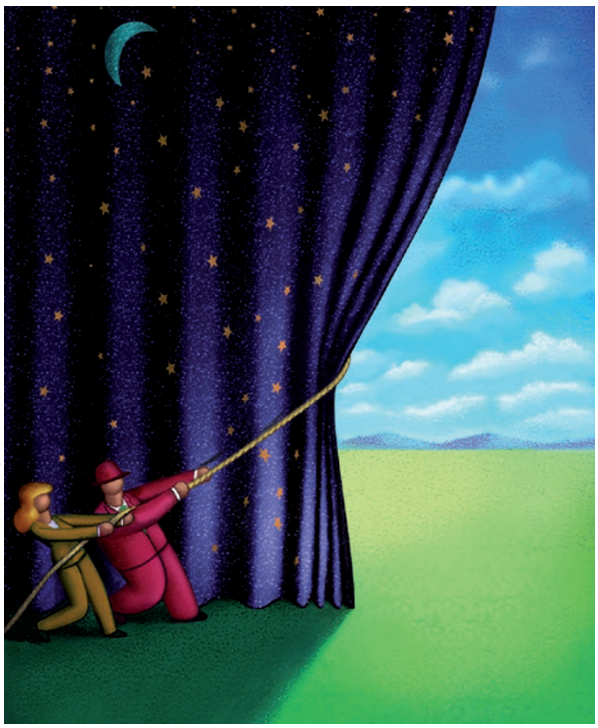
FIBROTIC DISEASES

New tools to target an elusive integrin

Most members of the integrin family of cell signalling molecules are well characterised and can be targeted by specific compounds, with the notable of exception of the integrin αVβ1. Now, Reed *et al.* report the rational development of small molecules to target this integrin and show potential therapeutic application in fibrotic diseases.



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Integrins — transmembrane receptors composed of an α-subunit and a β-subunit — are involved in a wide range of biological and pathological processes. A lack of suitable experimental tools, such as a heterodimer-specific antibody, has hindered research on αVβ1.

To design an inhibitor of αVβ1, Reed *et al.* used a base compound that is known to bind to the αV subunit in another integrin, αVβ3, to which they added a sulfonamidoproline moiety that was previously shown to bind to the β1 subunit in α2β1. Cocrystal structures of the ligand-binding regions of other integrins containing the αV or β1 subunits were used in computational models to further guide the design of the αVβ1-targeted inhibitor. Synthesized compounds were then tested in cell adhesion assays, and two small molecules, termed c8 and c6, that potently and specifically blocked αVβ1 were identified.

Through the use of immunoprecipitation of αV and western blotting for β1, the researchers found expression of the heterodimer in mouse and human lung fibroblasts, including those from patients with idiopathic pulmonary fibrosis (IPF).

The closely related integrins αVβ6 and αVβ8 bind to an amino-terminal fragment of latent transforming growth factor-β (TGFβ) in the extracellular matrix, leading to activation of the growth factor, which has a key role in fibrosis. Reed *et al.* found evidence of a similar mechanism for αVβ1, as cell lines expressing the integrin adhered to TGFβ, whereas cell lines lacking the integrin did not. Moreover, c8 potently and specifically inhibited activation of TGFβ by αVβ1-expressing cells, including fibroblasts from the lungs of patients with IPF. The authors note, however, that mechanisms independent of TGFβ could also be at play.

Finally, in mouse models of pathological hepatic or pulmonary fibrosis, subcutaneous administration of c8 after the establishment of fibrosis led to significant reductions in fibrosis compared with placebo-treated mice. Fluorescent staining of liver and lung tissue sections from c8-treated mice revealed downregulation of TGFβ signalling, supporting a role for αVβ1-mediated TGFβ activation in the antifibrotic effects of c8.

Together, the findings provide useful tools for further study of αVβ1 and highlight the therapeutic potential of targeting this signalling molecule in fibrotic diseases.

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ORIGINAL RESEARCH PAPER Reed, N. I. *et al.* The αvβ1 integrin plays a critical *in vivo* role in tissue fibrosis. *Sci. Transl. Med.* **7**, 288ra79 (2015)