

## Supplementary figures

**Supplementary figure 1 (Fig. S1):** PDE4 blockade has no effects on the proliferation of fibroblasts.

(A, B) Proliferation of fibroblasts from healthy individuals and SSc patients as assessed by CCK8 assay. In all experiments,  $N \geq 3$ . Statistical description: \* for  $0.01 < p < 0.05$ , \*\* for  $0.001 < p < 0.01$ , \*\*\* for  $p < 0.0001$ .

**Supplementary figure 2 (Fig. S2):** PDE4 blockade reduces tissue IL-6 levels in a preventative bleomycin model.

(A) Representative stainings of tissue IL-6. Images are shown in 200-fold magnification. (B) IgG isotype control. In all experiments,  $N \geq 7$ . Abbreviations: Veh., vehicle treated mice. Bleo, bleomycin treated mice.

**Supplementary figure 3 (Fig. S3):** PDE4 blockade has no effect on pro-fibrotic cytokine release from M1 macrophages.

(A-F) M1 macrophages from healthy volunteers and patients with diffuse-cutaneous SSc. (A-D) Messenger RNA expression of *iNOS* as well as *IL-6*, *IL-10*, *IL-13* and *TNF $\alpha$* . (E, F) IL-6 protein levels in the supernatants. (A-F) In all experiments,  $N \geq 10$ . Statistical description: \* for  $0.01 < p < 0.05$ , \*\* for  $0.001 < p < 0.01$ , \*\*\* for  $p < 0.0001$ .

**Supplementary figure 4 (Fig. S4):** PDE4 blockade interferes with the release of pro-fibrotic cytokines from pre-differentiated M2 macrophages

(A-F) M2 macrophages from healthy volunteers. (A-D) Messenger RNA expression of specific *ARGINASE* as well as *IL-6*, *IL-13*, *TGFβ1* and *TGFβ2*. (E, F) IL-6 protein levels in the supernatants. (A-F) In all experiments,  $N \geq 5$ . Statistical description: \* for  $0.01 < p < 0.05$ , \*\* for  $0.001 < p < 0.01$ , \*\*\* for  $p < 0.0001$ .

**Supplementary figure 5 (Fig. S5):** Knockdown of PDE4B specifically blocks the release of pro-fibrotic cytokines from macrophages undergoing M2 differentiation.

(A-C) M2 macrophages from healthy volunteers. Messenger RNA expression of specific *ARGINASE* as well as *IL-6*, *IL-13*, *TGFβ1* and *TGFβ2*. In all experiments,  $N \geq 8$ . Statistical description: \* for  $0.01 < p < 0.05$ , \*\* for  $0.001 < p < 0.01$ , \*\*\* for  $p < 0.0001$ .

**Supplementary figure 6 (Fig. S6):** Overview of treatment and control groups in the therapeutic model of bleomycin-induced dermal fibrosis.

**Supplementary figure 7 (Fig. S7):** PDE4 blockade reduces tissue IL-6 levels in a therapeutic bleomycin model.

(A) Representative stainings of tissue IL-6. Images are shown in 200-fold magnification. (B) IgG isotype control. In all experiments,  $N \geq 6$ . Abbreviations: Veh., vehicle treated mice. Bleo, bleomycin treated mice.

**Supplementary figure 8 (Fig. S8):** PDE4 blockade reduces tissue IL-6 levels in the topoisomerase I mouse model.

**(A)** Representative stainings of tissue IL-6. Images are shown in xx-fold magnification. **(B)** IgG isotype control. In all experiments,  $N \geq 6$ . Abbreviations: Veh., vehicle treated mice.

**Supplementary figure 9 (Fig. S9):** PDE4 blockade reduces tissue IL-6 levels in a sclerodermatous Graft-versus-Host-Disease.

**(A)** Representative stainings of tissue IL-6. Images are shown in xx-fold magnification. **(B)** IgG isotype control. In all experiments,  $N \geq 6$ . Abbreviations: Veh., vehicle treated mice.

Fig. S1

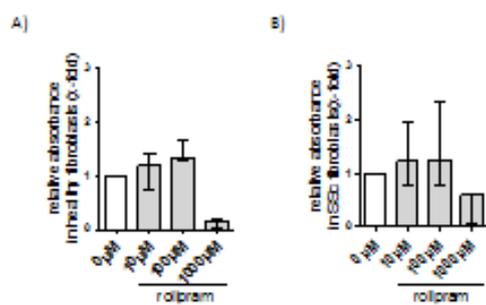


Fig. S2

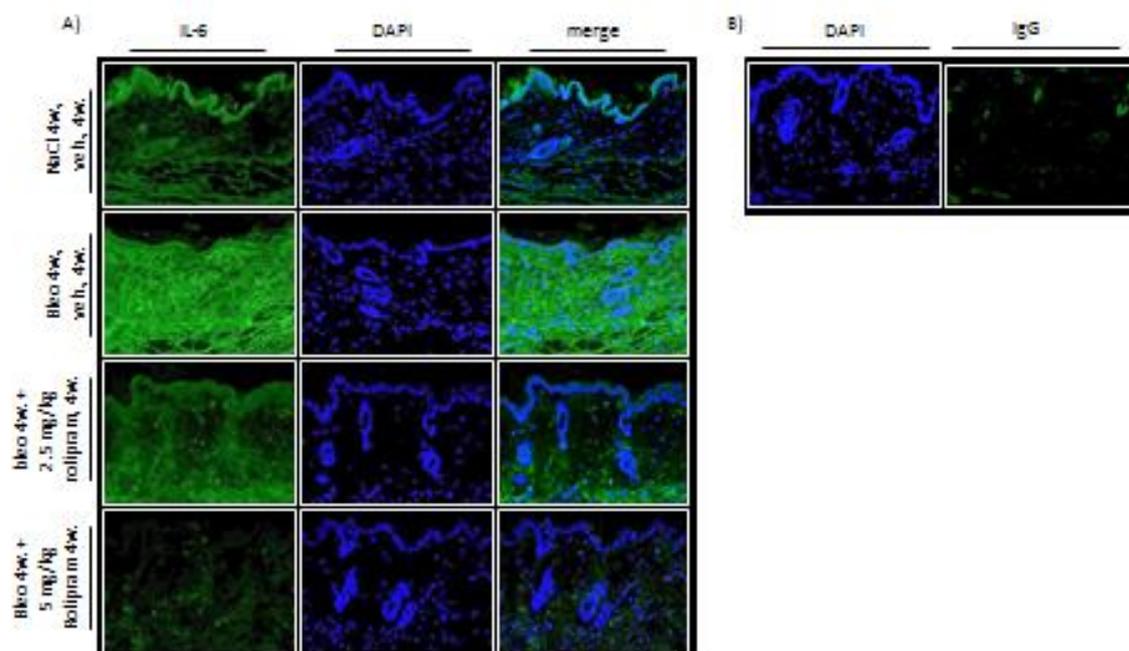


Fig. S3

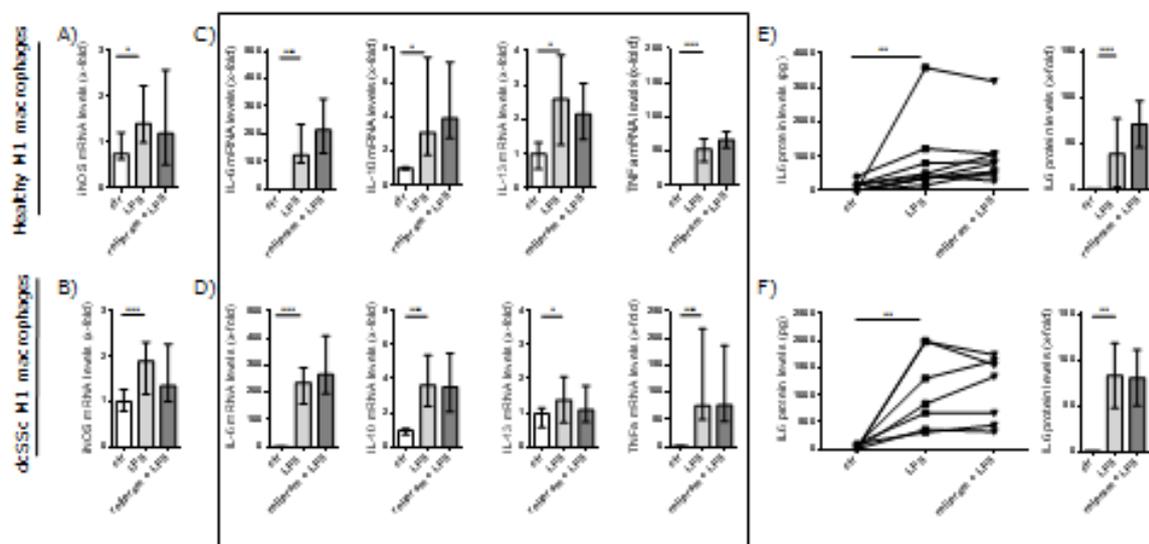


Fig. S4

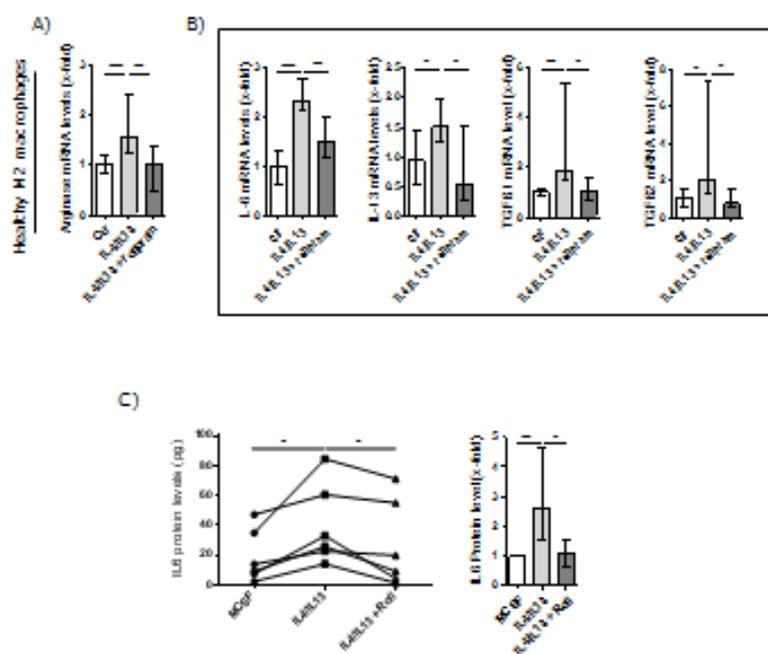


Fig. S5

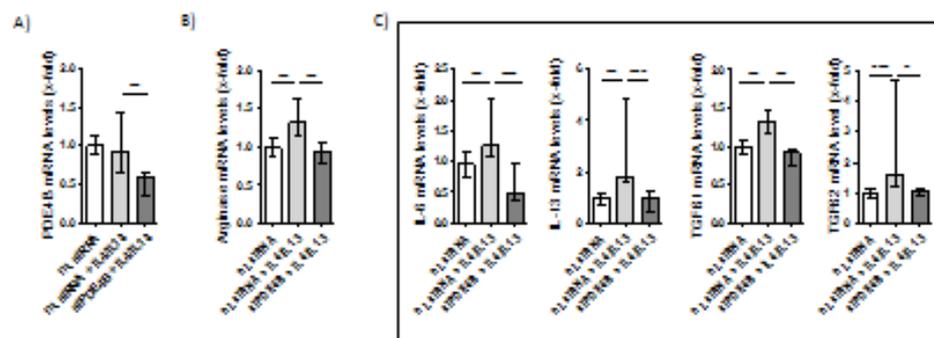


Fig. S6

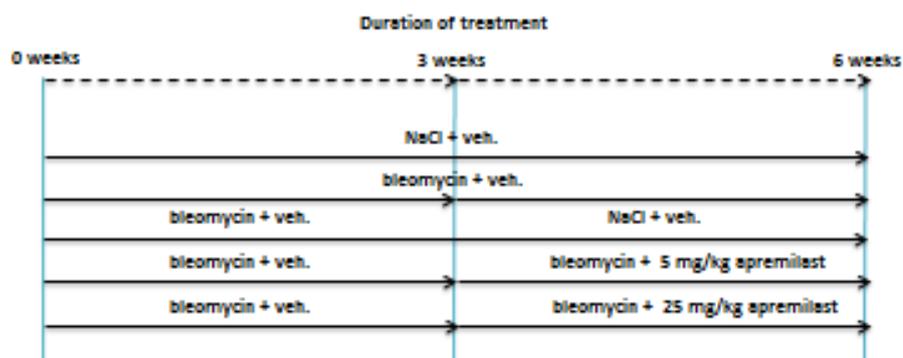




Fig. 5B

