**Supplemental figure 1.** EZH2 mRNA levels did not correlate with the modified Rodnan skin score.



**Supplemental figure 2.** DZNep dose-dependently reduced the expression of EZH2 and H3K27me3 in SSc fibroblasts.



**Supplemental figure 3.** GSK126 significantly inhibited wound closure in SSc fibroblasts at 10  $\mu$ M compared to untreated cells (NT). Experiments were performed in 2 patient cell lines with 6 replicates in each condition. The figure is representative from one patient cell line. Data was presented as mean ± SEM.



**Supplemental figure 4.** GSK126 prevented skin fibrosis in the bleomycin-skin fibrosis model in mice as indicated by hydroxyproline content and measurement of the dermal thickness. Data are presented as mean ± SD.









PBS

Bleomycin+Vehicle

Bleomycin+GSK126 (0.5mg/kg)

Bleomycin+GSK126 (5mg/kg)





**Supplemental figure 5.** EZH2 inhibitors GSK126 and DZNep reduced H3K27me3 levels in the bleomycin-skin fibrosis model in mice.



PBS

Bleomycin+Vehicle



Bleomycin+GSK126 (0.5mg/kg)



Bleomycin+GSK126 (5mg/kg)





PBS

Bleomycin+Vehicle



Bleomycin+DZNep

**Supplemental figure 6.** Relative mRNA expression of genes involved in Notch signaling in normal and SSc ECs. Data are expressed as fold change compared to mean of normal ECs.



**Supplemental figure 7.** Relative mRNA expression levels of genes involved in Notch signaling after EZH2 inhibition by DZNep ( $5\mu$ M, 48 hours) in SSc fibroblasts. Data are expressed as fold change compared to PBS-treated cells. ND=not detected.

