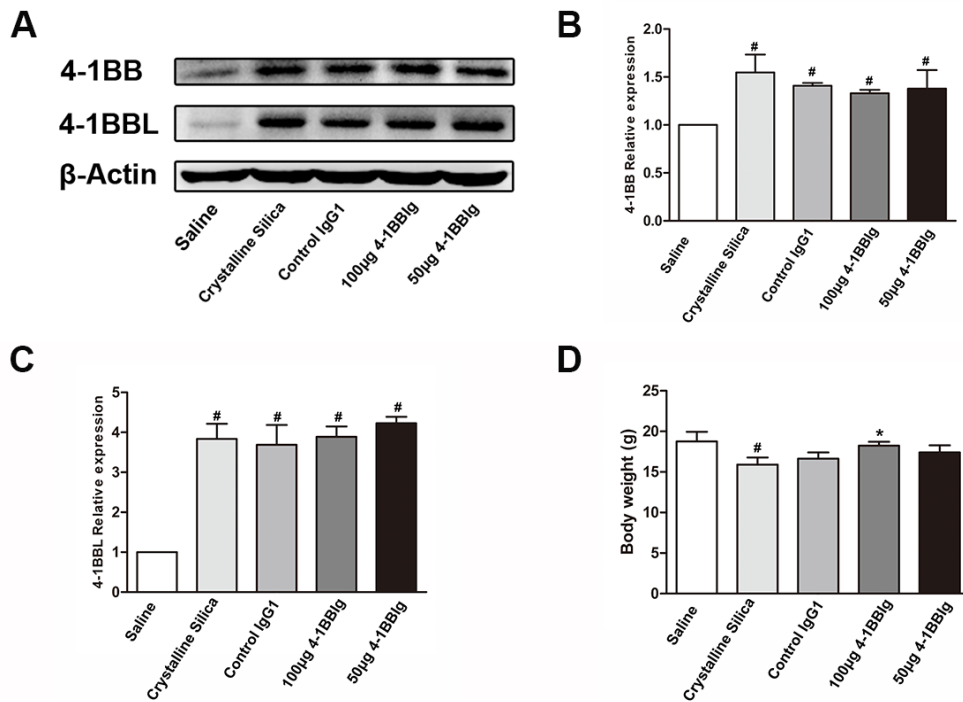
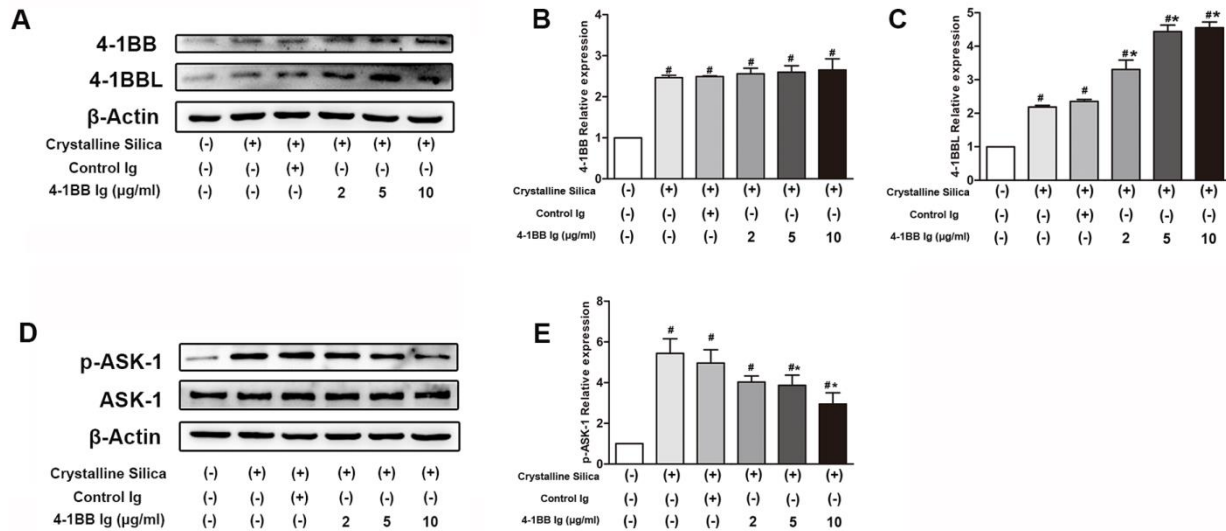


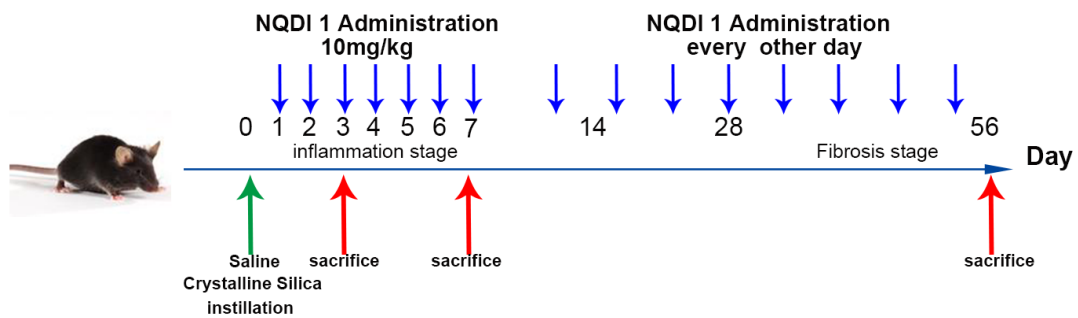
**Figure S1. The equivalent spherical diameter of crystalline silica used in the experiment.** The picture is a screen shot of the product data sheet. Datasheet link: <http://www.ussilica.com/sites/ussilica.com/uploads/files/product-data-sheets/industry/building-products/MINUSIL5-MillCreek.pdf>



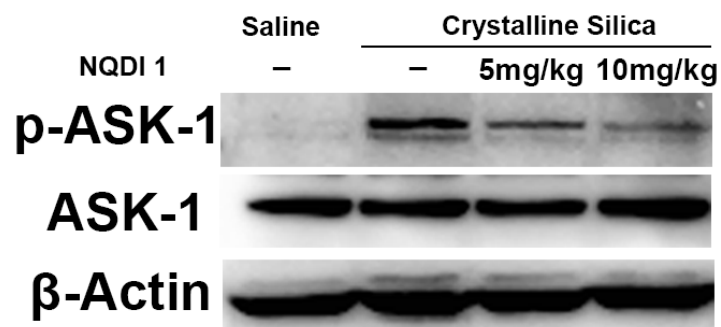
**Figure S2. The effects of 4-1BBIg on different treated mice.** **A** Western blot analysis of 4-1BB and 4-1BBL in the lungs from saline, crystalline silica, crystalline silica + 100µg control IgG1, crystalline silica + 100µg 4-1BBIg, and crystalline silica + 50µg 4-1BBIg treated mice. (n=3-4) The experiments were performed in triplicate. **B** The levels of 4-1BB were normalized to those of β-actin. Data are the mean of three independent experiments. **C** The levels of 4-1BBL were normalized to those of β-actin. Data are the mean of three independent experiments. **D** The body weights of treated mice at Day7. (n=3-4) # P<0.05 compared with the saline group; \* P<0.05 compared with the crystalline silica group. Error bars indicate the mean ± S.D.



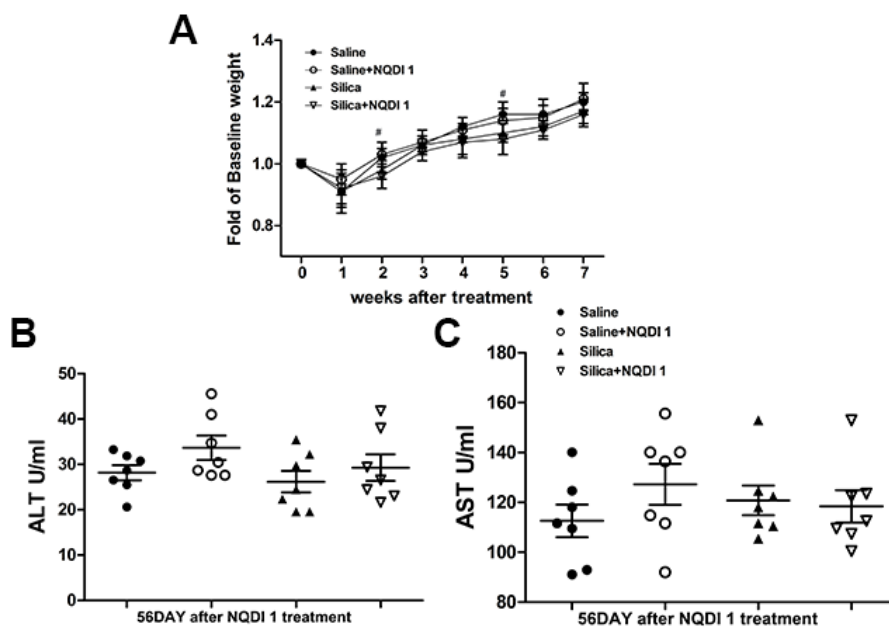
**Figure S3. Expressions of 4-1BB, 4-1BBL and p-ASK-1 in splenocytes of co-culture system.** **A** Western blot analysis of 4-1BB and 4-1BBL in splenocytes. Cells were stimulated with crystalline silica at various concentration of 4-1BB Ig. (n=3) **B C** The levels of 4-1BB and 4-1BBL were normalized to those of  $\beta$ -actin. Data are the mean of three independent experiments. Error bars indicate the mean  $\pm$  S.D. #  $P < 0.05$  compared with the saline group. \*  $P < 0.05$  compared with the crystalline silica group. **D** Western blot analysis of ASK-1 and p-ASK-1 in splenocytes. **E** The levels of p-ASK-1 were normalized to those of  $\beta$ -actin. Data are the mean of three independent experiments. Error bars indicate the mean  $\pm$  S.D. #  $P < 0.05$  compared with the saline group. \*  $P < 0.05$  compared with the crystalline silica group.



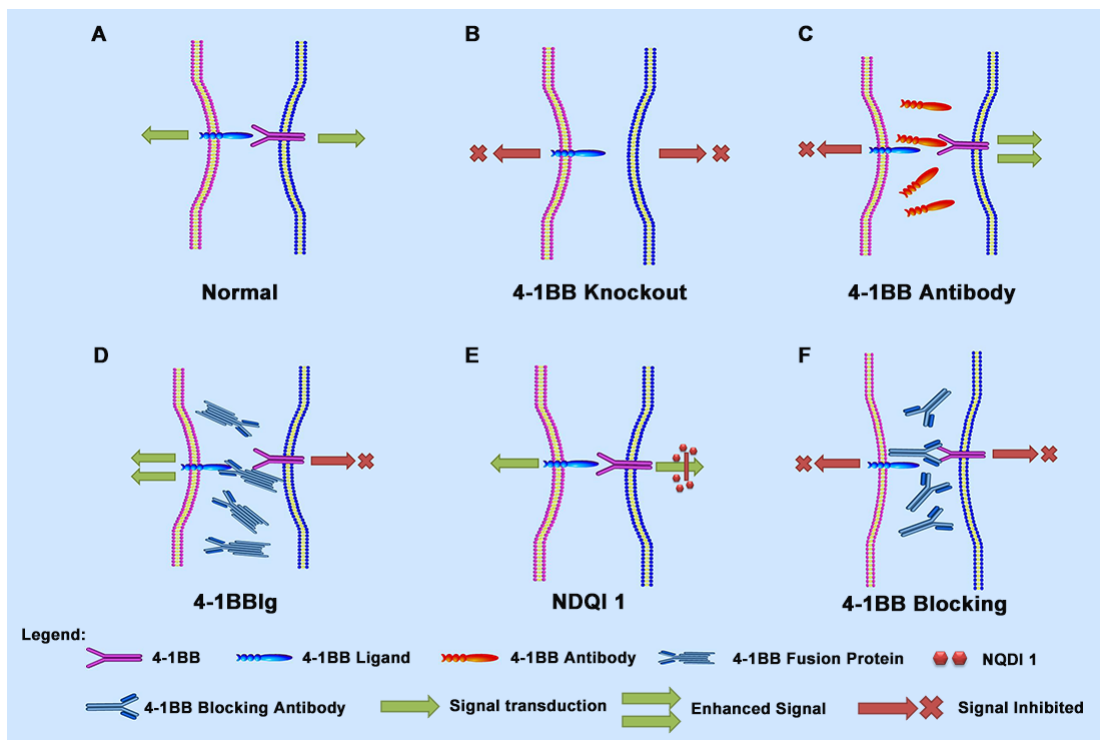
**Figure S4. Experimental protocol for the induction of silicosis and treatment scheme of NQDI 1.**



**Figure S5 The effects of different NQDI 1 concentrations on ASK-1 phosphorylation in the lungs.** Western analysis of ASK-1 and p-ASK-1 in the lungs of different treated mice. (n=3) The experiment was performed in triplicate.



**Figure S6 The effects of NQDI 1 on animals body weights and liver functions. A** animals body weights after NQDI 1 administration (n=10) **B C** AST and ALT levels in serum after treated (n=7). # P<0.05 compared with the saline group; \* P<0.05 compared with the crystalline silica group.



**Figure S7 Considerations of blocking 4-1BB pathway. A** Normal interaction between 4-1BB and 4-1BBL. Bidirectional signals are unobstructed. **B** Signals in 4-1BB knockout mice. Bidirectional signals are inhibited. **C** Signals after 4-1BB antibody administration. 4-1BBL signal inhibited, 4-1BB signal is enhanced and lasting. **D** Signals after 4-1BB Ig administration. 4-1BBL signal is enhanced and lasting, 4-1BB signal is inhibited. **E** Signals after NQDI 1 administration. Interaction between 4-1BB and 4-1BBL is normal. 4-1BBL signal is normal and 4-1BB signal is blocked by downstream kinase. **F** Signals after 4-1BB blocking antibody administration. Bidirectional signals are obstructed.