

## **Supplemental material**

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**Supplemental Figure 8.** Effects of a short-term therapeutic intervention with sGC activator BAY 54-6544 in lung and liver of *Cyb5r3* SPC-KO infected mice.

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**Supplemental Figure 10.** Therapeutic intervention with sGC agonists in the absence of injury.

**Supplemental Figure 11.** Therapeutic intervention with sGC agonists ameliorates fibrotic and senescence outcomes in *Cyb5r3* SPC-KO mice after injury at 28 days.

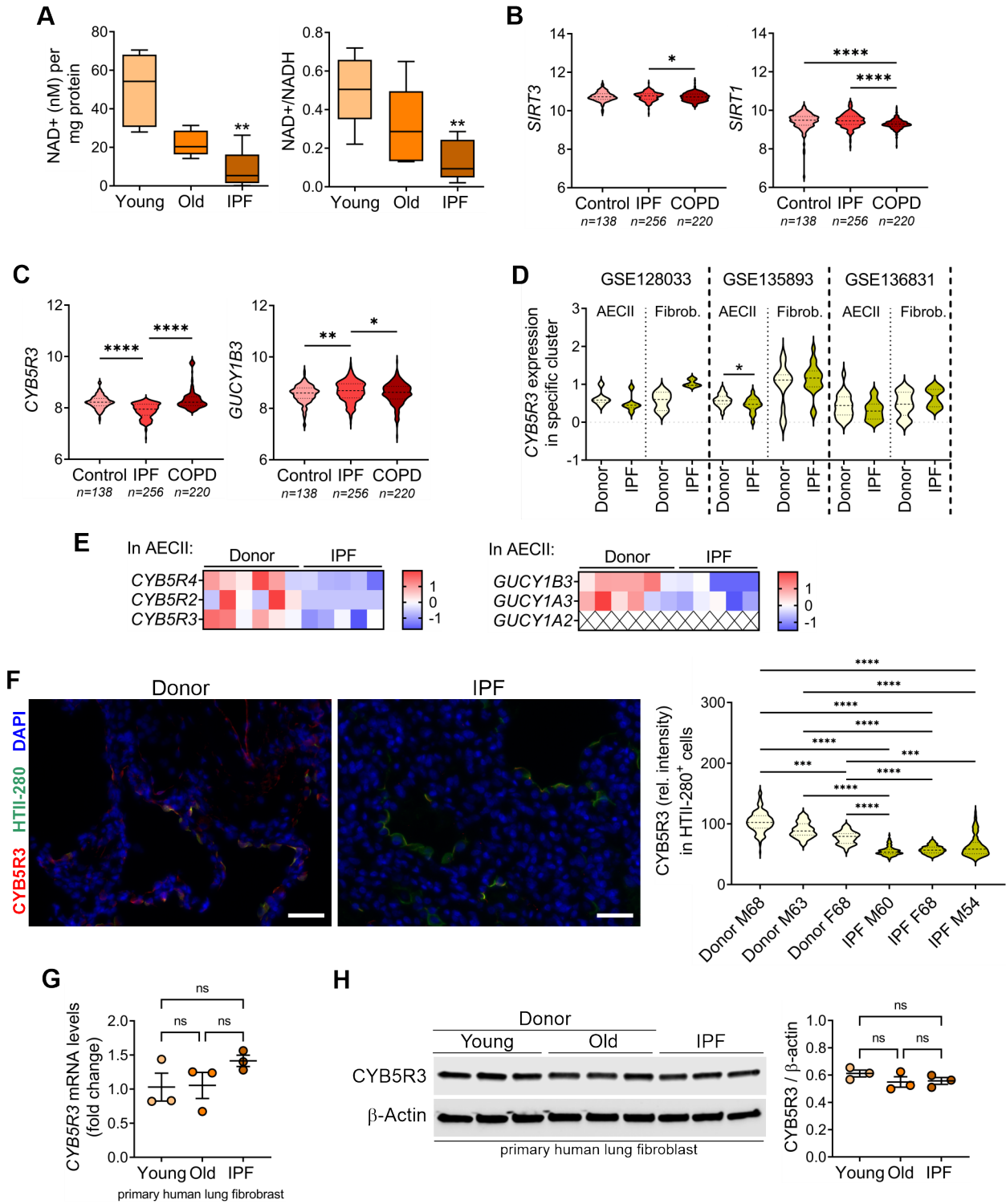
**Supplemental Figure 12.** CYB5R3 deficiency is associated with oxidative stress and a pro-fibrotic phenotype.

**Supplemental Figure 13.** CYB5R3 modulates expression of TGF- $\beta$ 1-target genes via sGC-dependent pathways.

**Supplemental Figure 14.** Effects of sGC agonists on primary mouse lung fibroblasts in culture.

**Supplemental Table 1.** Demographic characteristics of the patients cohort.

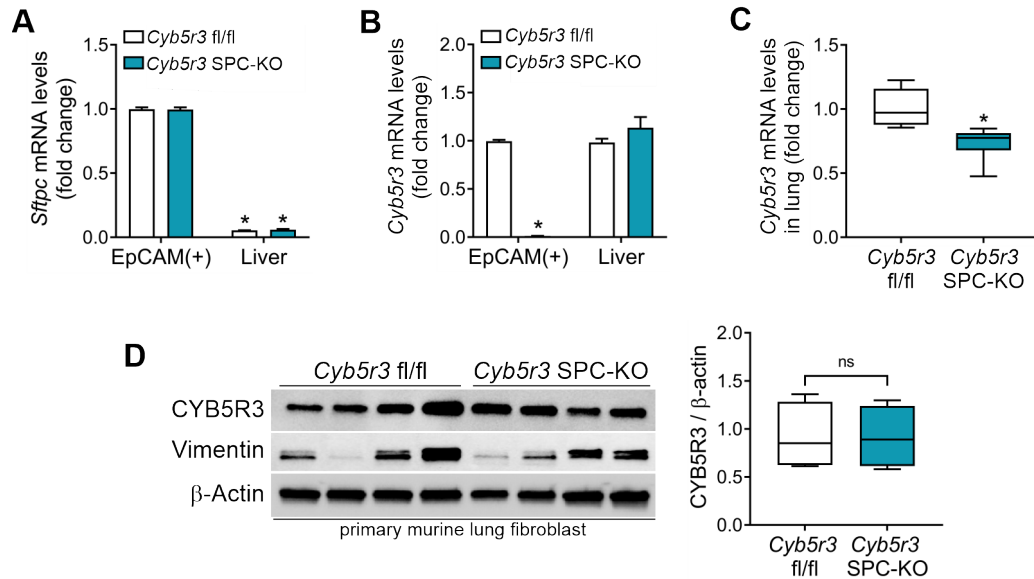
**Supplemental Table 2.** List of PrimeTime® primer assays (Integrated DNA Technologies)



**Supplemental Figure 1. Levels of NAD<sup>+</sup> consuming and generating enzymes in different compartments of the fibrotic lung. (A)** Levels of normalized NAD<sup>+</sup> and NAD<sup>+</sup>/NADH ratio are reduced with age and in IPF lung compared with young donors

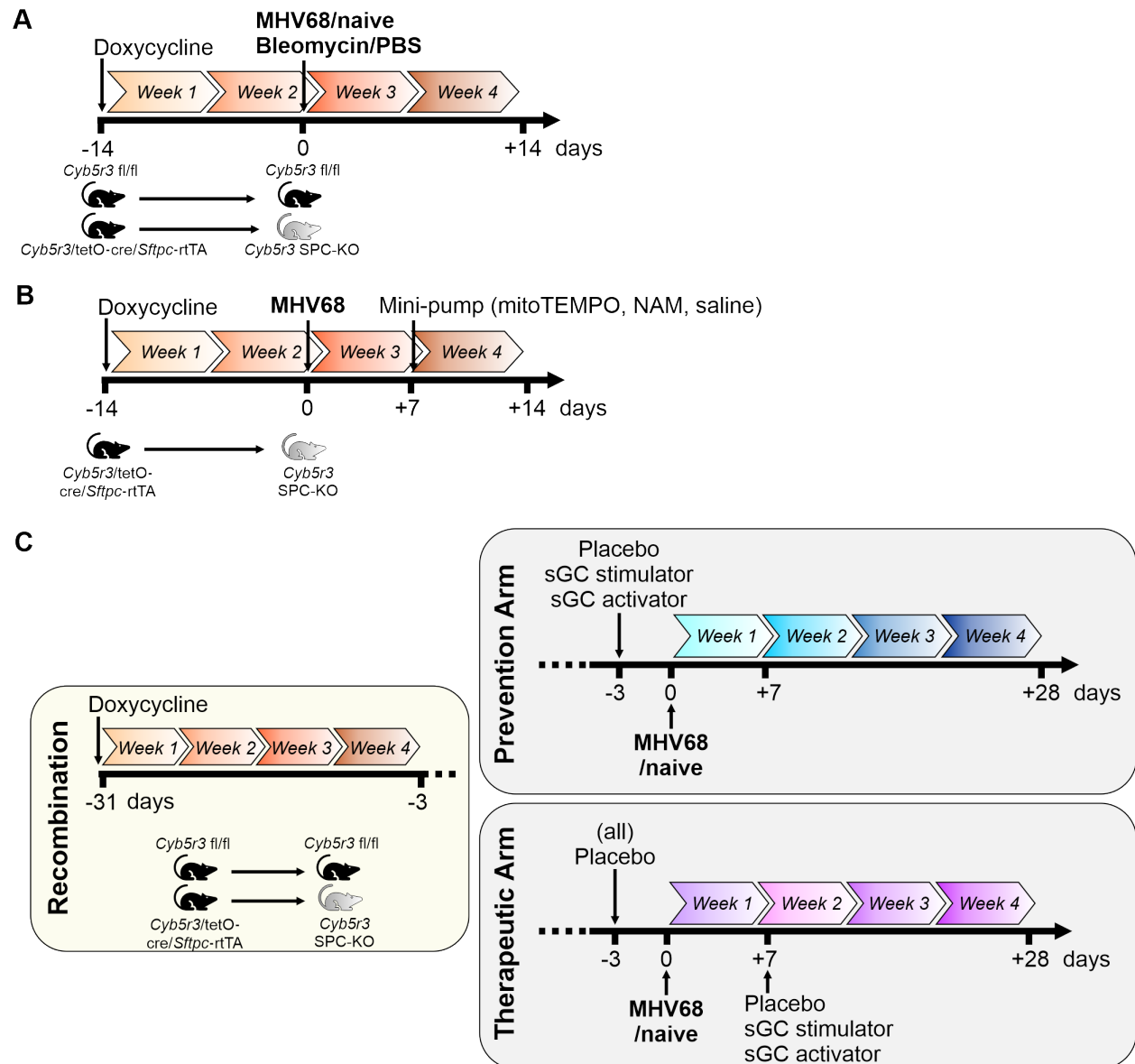
(Min-to-max with median,  $n = 5/\text{group}$ ). Relative gene expression levels of *SIRT3* and *SIRT1* (**B**) and *CYB5R3* and *GUCY1B3* (**C**) on a large mRNA bulk expression dataset containing ILD and COPD patients and healthy controls from the Lung Tissue Research Consortium (Violin plots with median and quartiles;  $n = 91$  donor / 194 ILD / 144 COPD in GSE47460). See reference (24) (**D**) Mean *CYB5R3* expression in AECII and fibroblast clusters from three different scRNA-seq studies comparing donor and IPF lung. (Violin plots with median and quartiles;  $n = 6$  donor / 7 IPF in GSE128033;  $n = 32$  donor / 28 IPF in GSE135893;  $n = 18$  donor / 10 IPF in GSE136831). See reference (63) for data compilation. (**E**) Heatmap analysis of other *CYB5R* and *GUCY1* isoforms in AECII in scRNA-seq data from donor and IPF patients (GSE128033). Color scale denotes Z-score of the normalized fold change expression. (**F**) Different representative immunofluorescence using anti HTII-280 (AECII marker; green) and anti-CYB5R3 (red) antibodies ( $n = 3/\text{group}$ ). Scale bars: 50  $\mu\text{m}$ . Individual quantification of the different samples of CYB5R3 staining (as relative pixel intensity) of individual AECII (HTII-280+) cells per condition. (Violin plots with median and quartiles). CYB5R3 transcript (**G**) and protein levels (**H**) in primary lung fibroblasts isolated from young and old donors, and IPF lungs (Individual data with mean  $\pm$  SEM,  $n = 3/\text{group}$ ). Statistical analysis was performed using 1-way ANOVA with multiple comparison test (A-C, F-G) and unpaired, 2-tailed Student's t test (D); ns, no significant; \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ , \*\*\*\* $p < 0.0001$ .



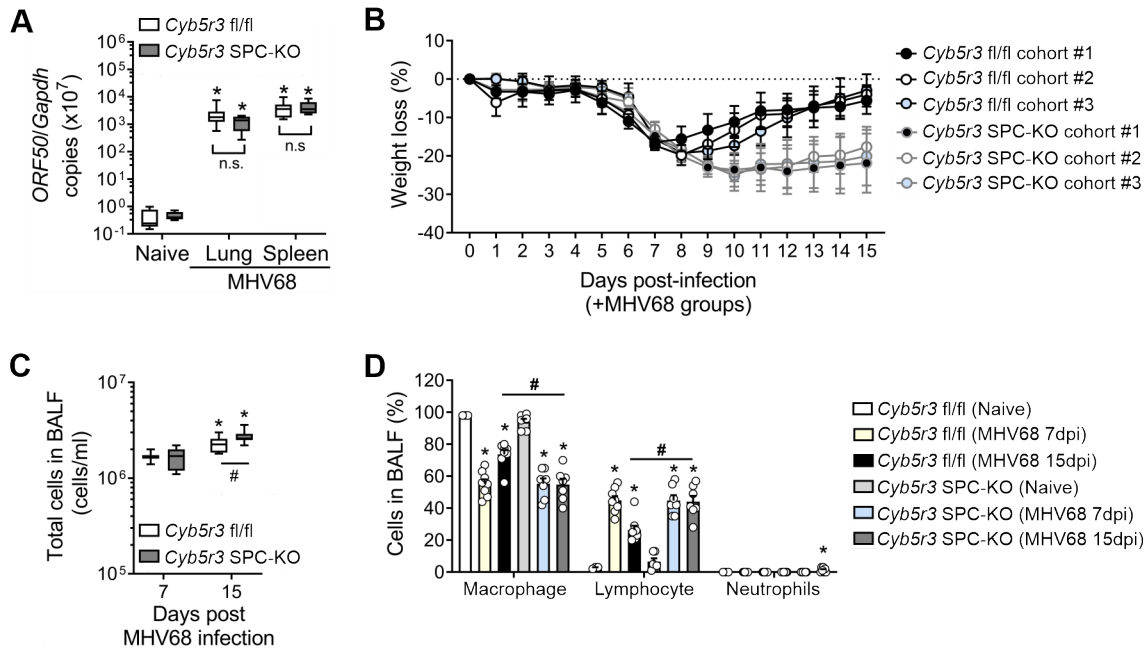


**Supplemental Figure 2. Confirmation of *Cyb5r3* deletion in murine AECIIs.** (A) Enrichment of AECII from *Cyb5r3* fl/fl and *Cyb5r3* SPC-KO mice lungs was performed and levels of *Sftpc* were tested. (Data are reported as mean  $\pm$  SEM,  $n = 3$ /group). (B) In the enriched fraction, cells derived from *Cyb5r3* SPC-KO lungs did not express *Cyb5r3* transcript at a detectable level. (Data are reported as mean  $\pm$  SEM,  $n = 3$ /group). (C) Total lung lysate from conditional type II lung epithelial cells *Cyb5r3* knockout mice show less expression of *Cyb5r3* mRNA. (Min-to-max with median,  $n = 6$ /group). (D) Representative immunoblot and quantification of CYB5R3 transcript in primary lung fibroblasts isolated from *Cyb5r3* fl/fl and *Cyb5r3* SPC-KO mice lungs. Using vimentin as fibroblast fraction marker. (Min-to-max with median,  $n = 4$ /group).

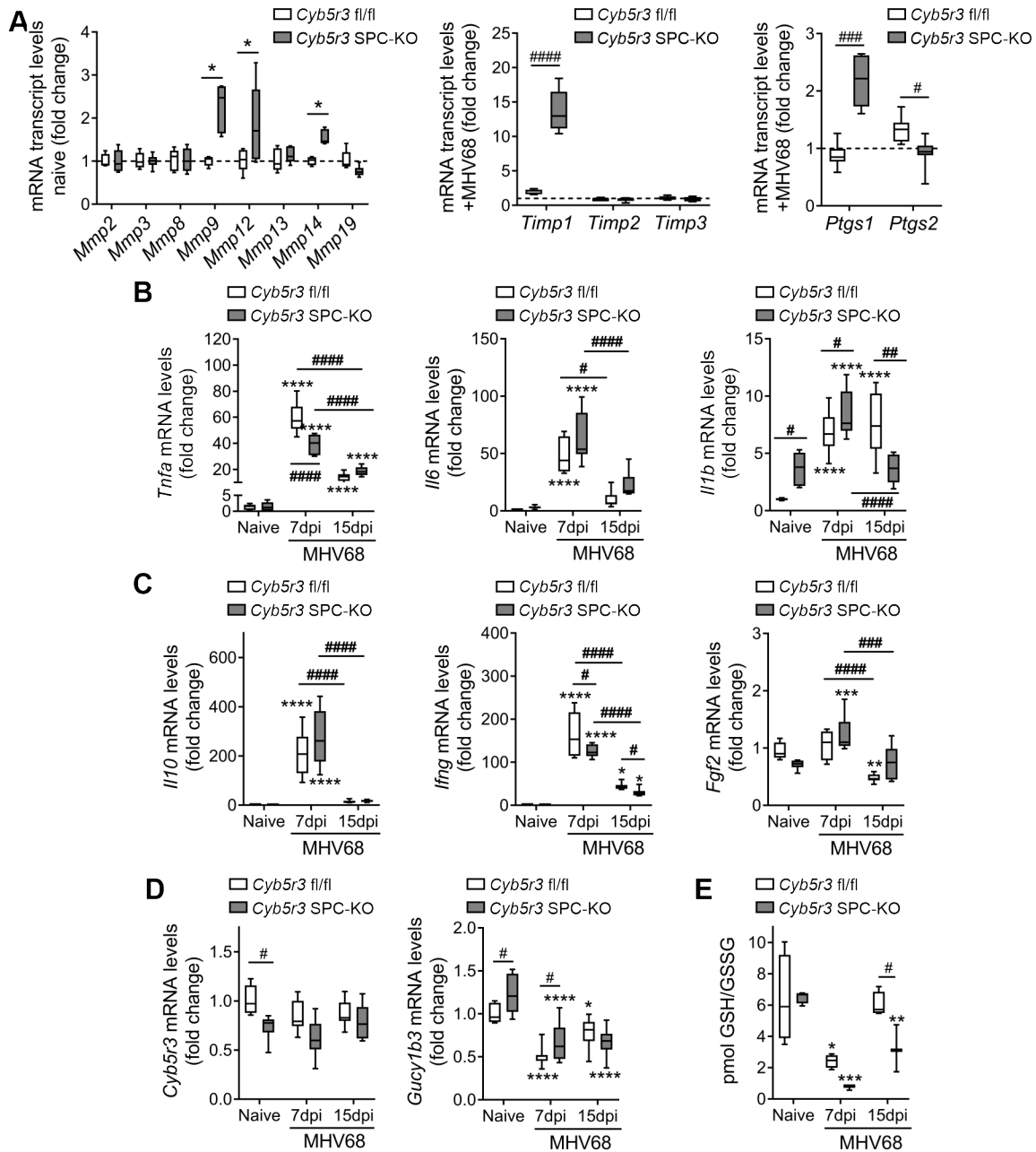
Statistical analysis was performed using 2-way ANOVA with multiple comparison test (A-B), 2-tailed Student's t test (C-D); \* $p < 0.05$ ; n.s., non-significant.



**Supplementary Figure 3. Schematics of the in vivo experiments performed. (A)** MHV68 and bleomycin models of lung injury and fibrosis. **(B)** Mitochondrial therapeutic intervention in MHV68 model. **(C)** Preventive and therapeutic interventions using sGC agonists (sGC stimulator BAY 41-8543 or sGC activator 54-6544) in MHV68 model.

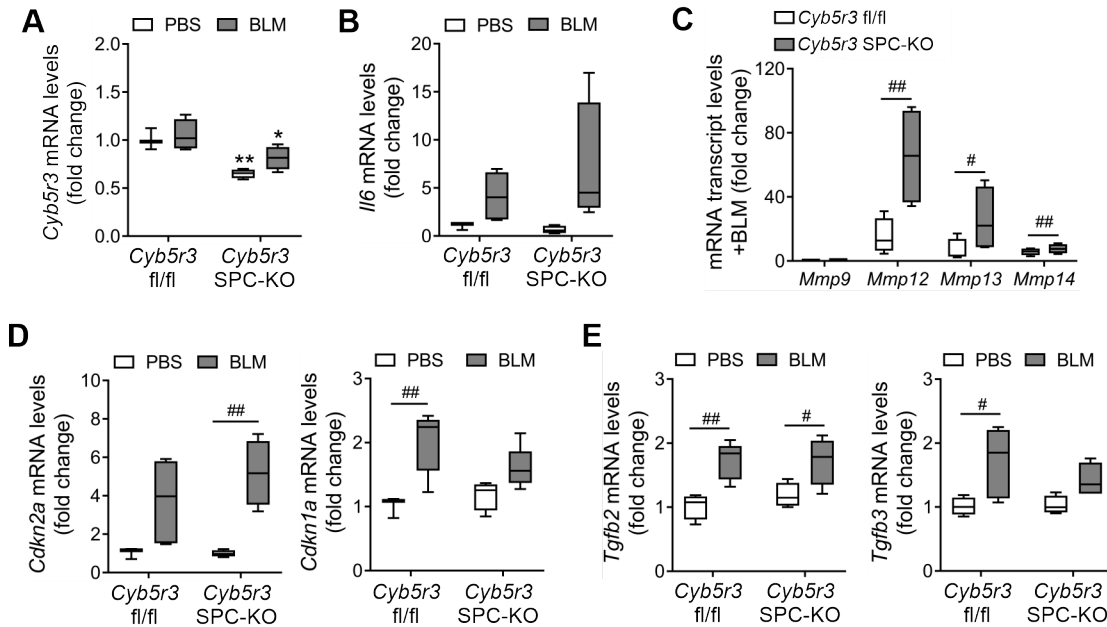


**Supplemental Figure 4. Reproducibility of the MHV68-induced lung fibrosis model in *Cyb5r3* SPC-KO mice.** (A) Viral load by qPCR from *Cyb5r3* fl/fl and *Cyb5r3* SPC-KO mice at 15 days post-infection. (Min-to-max with median,  $n = 6-8/\text{group}$ ). (B) Weight loss data in *Cyb5r3* fl/fl and *Cyb5r3* SPC-KO mice after MHV68 infection performed as three different cohorts (started on different dates at different locations in the vivarium). (Data point is mean  $\pm$  SD,  $n = 6$ ). Total cell numbers (C) and differential cells populations (D) in the BALF (bronchoalveolar lavage fluid) at different time points after MHV68 infection. (C: Min-to-max with median,  $n = 6-8/\text{group}$ ; D: Individual values with mean  $\pm$  SEM,  $n = 6-8/\text{group}$ ). Statistical analysis was performed using 2-way ANOVA with multiple comparison test (A, C-D), and 1-way repeated measures ANOVA (B); versus naïve: \* $p<0.05$ ; as indicated: # $p<0.05$ ; n.s., non-significant.

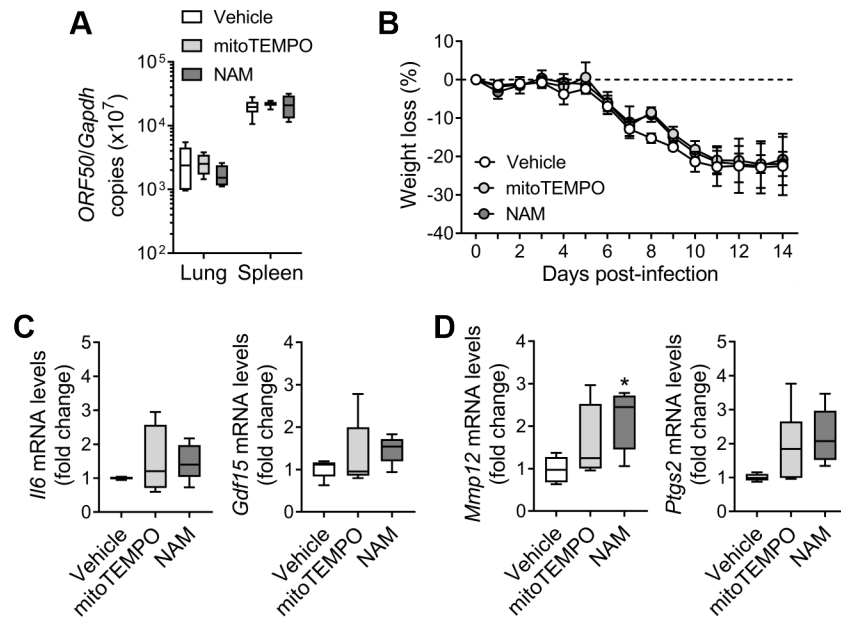


**Supplemental Figure 5. Other markers of fibrosis, inflammation, and injury in the MHV68-induced lung fibrosis model in *Cyb5r3* SPC-KO mice.** (A) Changes in the relative transcript levels of different *Mmps* in the naïve lung. Relative changes of the different *Timps* and *Ptgs* isoforms upon MHV68 infection. (Min-to-max with median,  $n = 6-8/\text{group}$ ). (B) Relative expression changes of inflammation markers *Tnfa*, *Il6* and *Il1b* mRNA levels after virus infection in *Cyb5r3* fl/fl and *Cyb5r3* SPC-KO mice. (Min-to-max

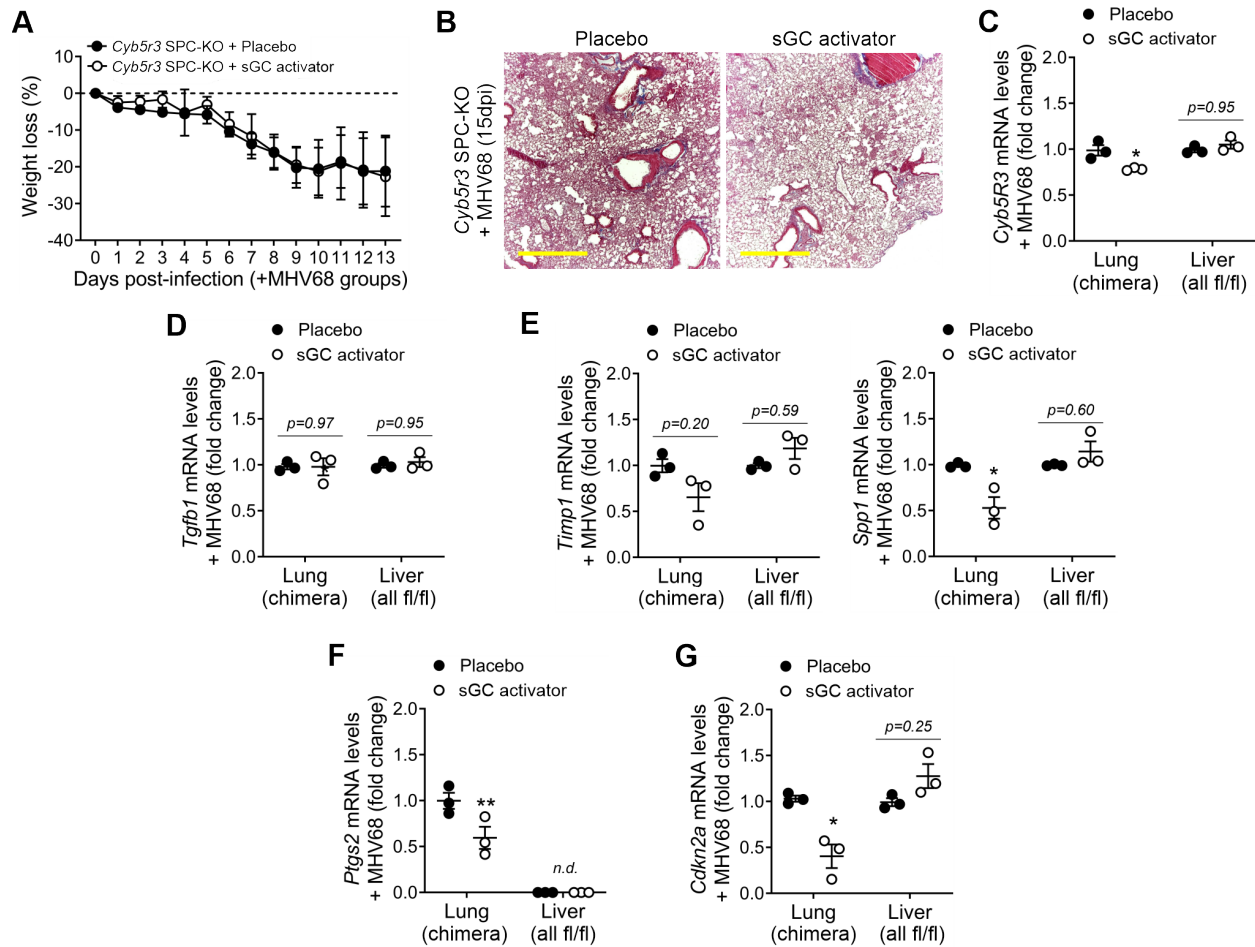
with median,  $n = 6-8/\text{group}$ ). (C) Relative expression changes of injury markers *Il10*, *Ifng* and *Fgf2* mRNA levels after virus infection. (Min-to-max with median,  $n = 6-8/\text{group}$ ). (D) Transcript changes upon infection in *Cyb5r3* and *Gucy1b3* in *Cyb5r3* fl/fl and *Cyb5r3* SPC-KO mice. (Min-to-max with median,  $n = 6-8/\text{group}$ ). (E) The ratio of reduced (GSH) and oxidized (GSSG) glutathione levels in *Cyb5r3* fl/fl and *Cyb5r3* SPC-KO mouse lungs after infection. (Min-to-max with median,  $n = 6-8/\text{group}$ ). Statistical analysis was performed using 2-way ANOVA with multiple comparison test (A-E), and unpaired, 2-tailed Student's t test (A); versus naïve: \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ , \*\*\*\* $p < 0.0001$ ; as indicated: # $p < 0.05$ , ## $p < 0.01$ , ### $p < 0.001$ , #### $p < 0.0001$ .



**Supplemental Figure 6. Increased expression of markers of fibrosis and senescence in the lung of the *Cyb5r3* SPC-KO mice after bleomycin.** (A) *Cyb5r3* transcript levels after bleomycin in total lung lysate. (Min-to-max with median,  $n = 4-5/\text{group}$ ). (B) Relative expression changes of SASP markers *Il6* mRNA levels after bleomycin in *Cyb5r3* fl/fl and *Cyb5r3* SPC-KO mice. (Min-to-max with median,  $n = 4-5/\text{group}$ ). (C) Relative expression of different *Mmps* transcripts after bleomycin treatment in *Cyb5r3* fl/fl and *Cyb5r3* SPC-KO mice. (Min-to-max with median,  $n = 4-5/\text{group}$ ). (D) Relative expression of senescence associated transcripts *Cdkn2a* and *Cdkn1a* after bleomycin treatment in *Cyb5r3* fl/fl and *Cyb5r3* SPC-KO mice. (Min-to-max with median,  $n = 4-5/\text{group}$ ). (E) Relative expression of *Tgfb2* and *Tgfb3* transcripts after bleomycin treatment in *Cyb5r3* fl/fl and *Cyb5r3* SPC-KO mice. (Min-to-max with median,  $n = 4-5/\text{group}$ ). Statistical analysis was performed using 2-way ANOVA with multiple comparison test (A-B, D-E) and unpaired, 2-tailed Student's t test (C); versus PBS: \* $p<0.05$ , \*\* $p<0.01$ ; as indicated: # $p<0.05$ , ## $p<0.01$ .



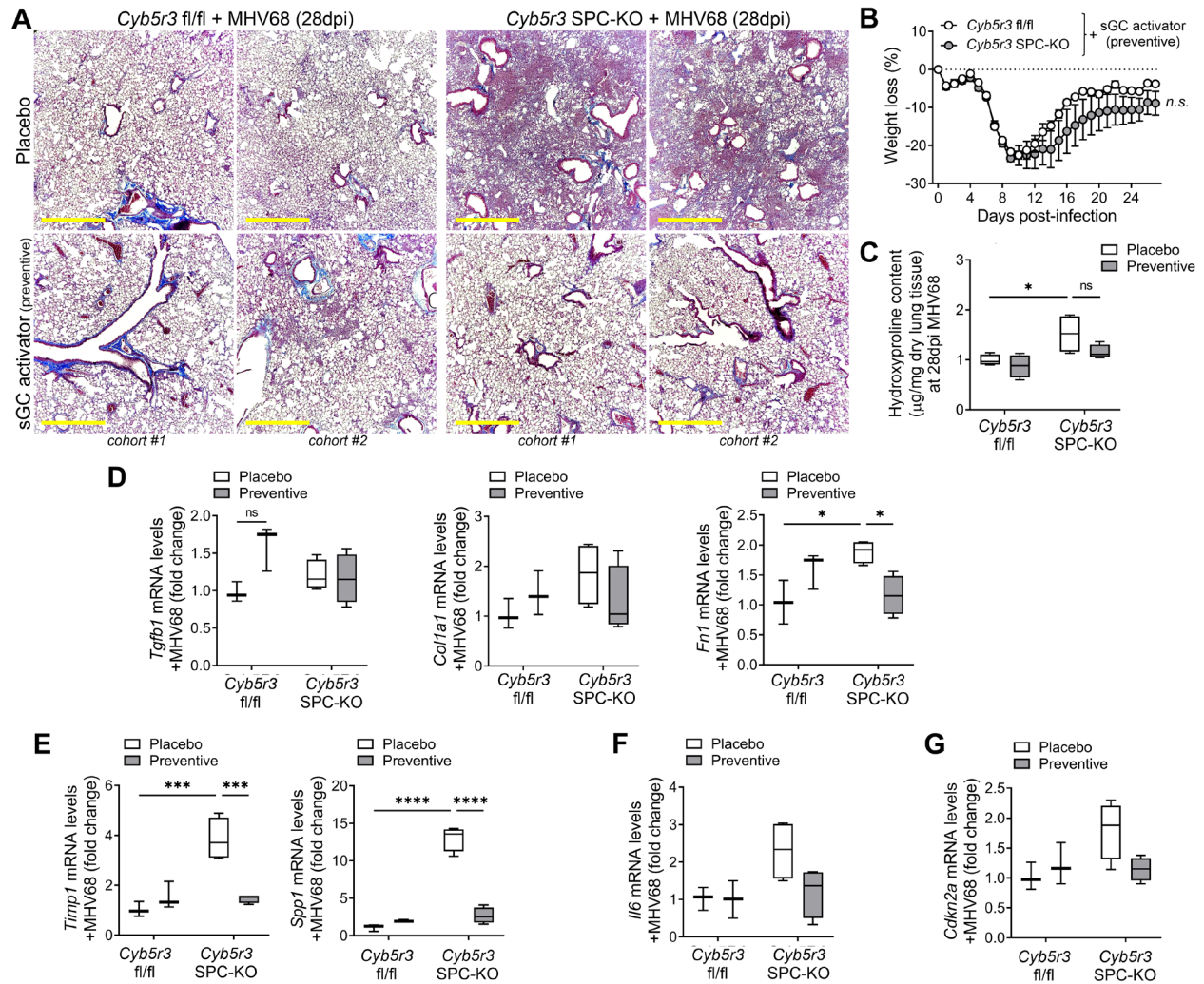
**Supplemental Figure 7. Mitochondrial intervention does not improve virus-induced lung fibrosis in *Cyb5r3* SPC-KO mice.** (A) Viral load by qPCR from the differently treated *Cyb5r3* SPC-KO mice at 15 days post-infection. (Min-to-max with median,  $n = 5-6$ /group). (B) Weight loss data of the three different treatment groups followed for 15 days post infection. Osmotic pump implantation was performed on day 7 after infection. (Data point is mean  $\pm$  SD,  $n = 6$ ). (C) No detectable change of *Il6* and *Gdf15* transcript levels after treatments in *Cyb5r3* SPC-KO MHV68-infected mice. (Min-to-max with median,  $n = 5-6$ /group). (D) Relative expression changes of profibrotic markers *Mmp12* and *Ptgs2* mRNA levels after treatments in *Cyb5r3* SPC-KO MHV68-infected mice. (Min-to-max with median,  $n = 5-6$ /group). Statistical analysis was performed using 1-way ANOVA with multiple comparison test (A, C-D) and 1-way repeated measures ANOVA (B); versus vehicle: \* $p < 0.05$ .



**Supplemental Figure 8. Effects of a short-term therapeutic intervention with sGC activator BAY 54-6544 in lung and liver of *Cyb5r3* SPC-KO infected mice.** (A) Weight loss data comparing AECII CYB5R3 deficient mice after infection in the different treatment arms (Placebo vs. sGC activator BAY 54-6544). (Data point is mean  $\pm$  SD,  $n = 3$ /group). (B) Representative Masson trichrome staining in lung sections *Cyb5r3* SPC-KO mice at day 14 post MHV68 infection with different intervention. Scale bars: 500  $\mu$ m. ( $n = 3$ /group). Change in transcript levels of *Cyb5r3* (C) and *Tgfb1* (D) after treatment in *Cyb5r3* SPC-KO MHV68-infected mice. (Individual data with mean  $\pm$  SEM,  $n = 3$ /group). (E) Levels of mRNA of *Timp1* and *Spp1* after treatment in lung and liver of *Cyb5r3* SPC-KO MHV68-infected mice. (Individual data with mean  $\pm$  SEM,  $n = 3$ /group). Change in transcript levels

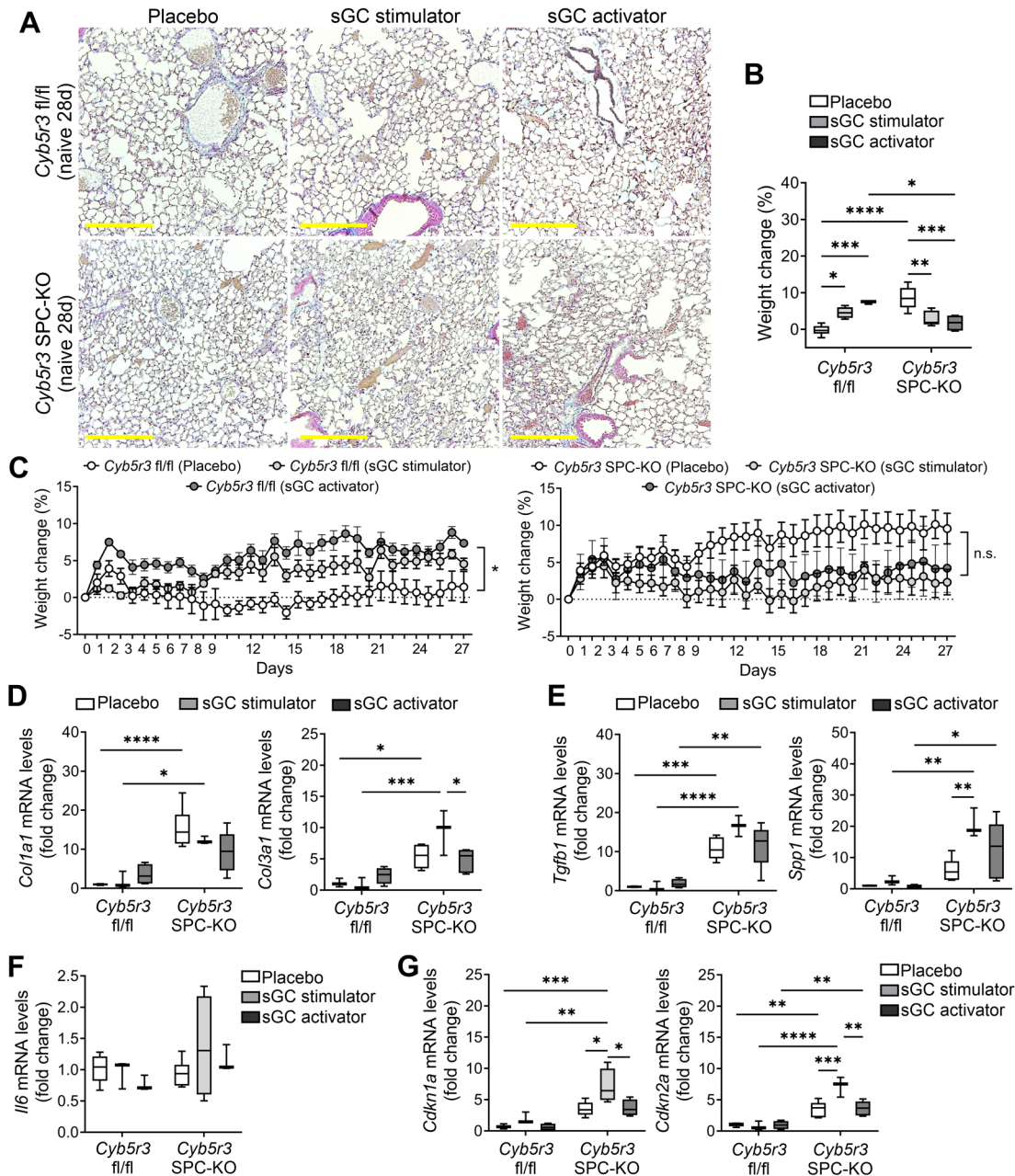


of *Ptgs2* (**F**) and *Cdkn2a* (**G**) after treatment in *Cyb5r3* SPC-KO MHV68-infected mice. (Individual data with mean  $\pm$  SEM,  $n = 3$ /group). Statistical analysis was performed using 1-way repeated measures ANOVA (A), and 2-way ANOVA with multiple comparison test (C-G); as indicated: \* $p < 0.05$ , \*\* $p < 0.01$ ; n.d., non-detected. Chimera: total lung lysate will be a mixture of KO and WT (fl/fl) cells.



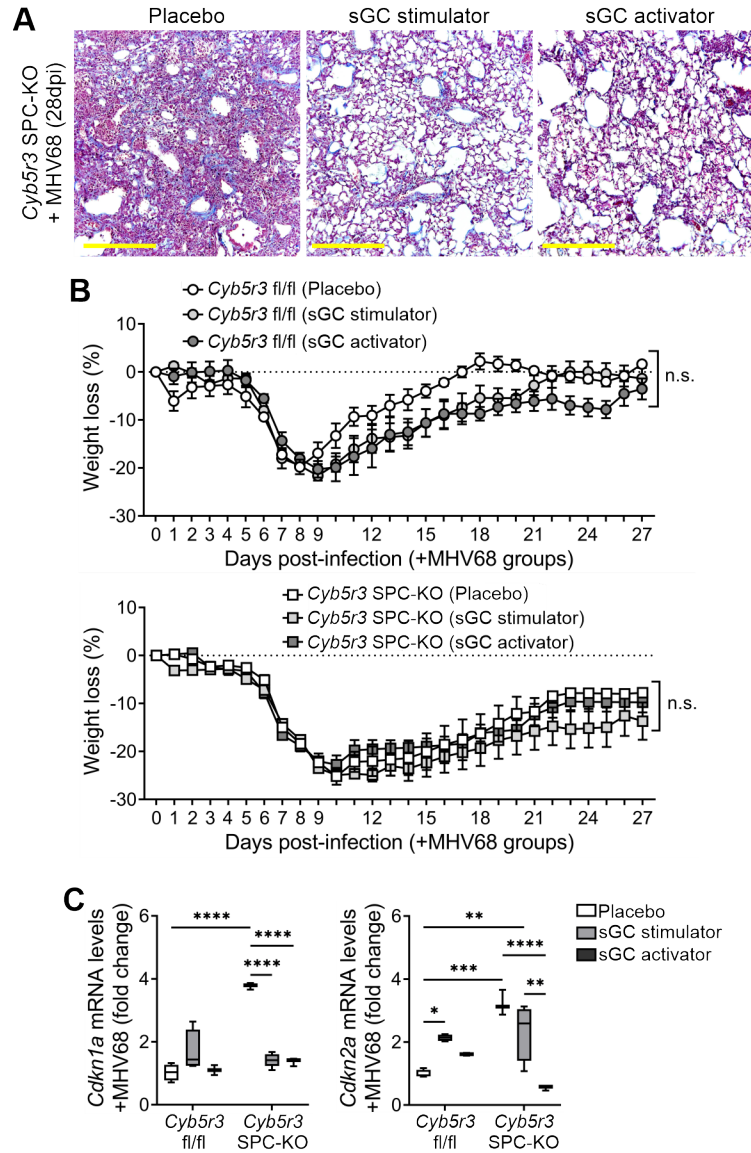
**Supplemental Figure 9. Preventive intervention with sGC activator ameliorates fibrotic endpoints in *Cyb5r3* SPC-KO mice after MHV68-induced lung fibrosis at day 28.** (A) Representative Masson trichrome staining in lung sections from *Cyb5r3* fl/fl and *Cyb5r3* SPC-KO mice at day 28 post MHV68 infection with different interventions representing different experimental cohorts (Placebo vs. sGC activator BAY 54-6544 diet). All interventions were administered mixed in the same base chow composition as the Placebo diet and started 3 days before the MHV68 infection took place. Scale bars: 500 μm. ( $n = 4-6/\text{group}$ ) (B) Weight loss data comparing fl/fl and AECII CYB5R3 deficient mice after infection in the activator preventive treatment arm. (Data point is mean  $\pm$  SD,

*n* = 4-6). **(C)** Collagen deposition in lungs of *Cyb5R3* fl/fl and *Cyb5R3* SPC-KO infected mice after the preventive intervention with sGC activator determined by hydroxyproline levels. (Min-to-max with median, *n* = 4-6/group). **(D)** Relative expression changes of fibrotic markers *Tgfb1*, *Col1a1* and *Fn1* mRNA levels after preventive treatment in *Cyb5R3* fl/fl and *Cyb5R3* SPC-KO MHV68-infected mice. (Min-to-max with median, *n* = 4-6/group). **(E)** Change in transcript levels of *Timp1* and *Spp1* after treatments in *Cyb5R3* fl/fl and *Cyb5R3* SPC-KO MHV68-infected mice after preventive treatment. (Min-to-max with median, *n* = 4-6/group). Change in transcript levels of *Il6* **(F)** and *Cdkn2a* **(G)** after preventive intervention with sGC activator in *Cyb5R3* fl/fl and *Cyb5R3* SPC-KO MHV68-infected mice. (Min-to-max with median, *n* = 4-6/group). Statistical analysis was performed using 1-way repeated measures ANOVA (B), and 2-way ANOVA with multiple comparison test (C-G); as indicated: \**p*<0.05, \*\*\**p*<0.001, \*\*\*\**p*<0.0001; n.s., non-significant.



**Supplemental Figure 10. Therapeutic intervention with sGC agonists in the absence of injury.** (A) Representative Masson trichrome staining in lung sections from *Cyb5R3* fl/fl and *Cyb5R3* SPC-KO mice at day 28 with different interventions (Placebo, sGC stimulator BAY 41-8543 or sGC activator BAY 54-6544). All interventions were administered mixed in the same base chow composition as the Placebo diet and started at day 7. Scale bars: 500  $\mu$ m. (*n* = 5-6/ group). (B) Percentage of weight change

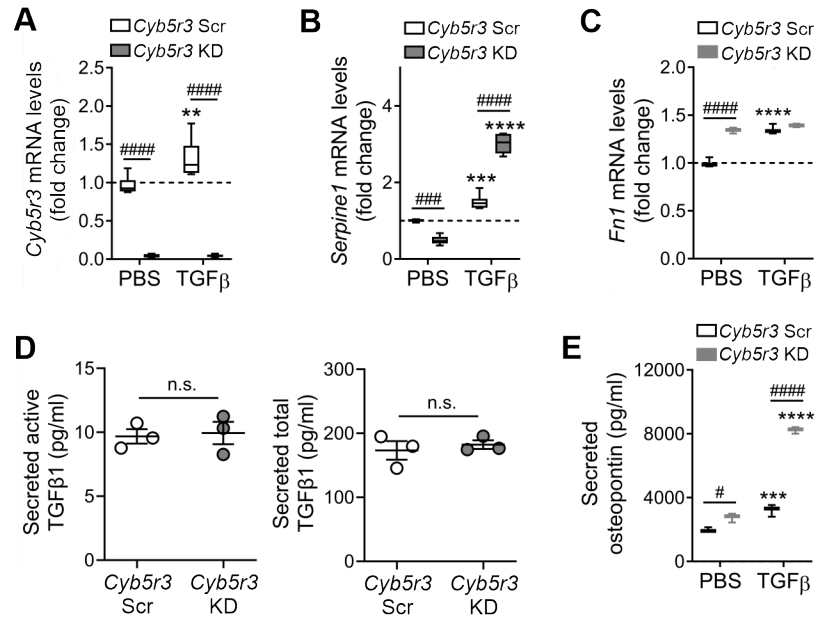
comparing naïve fl/fl mice in the different treatment arms. (Data point is mean  $\pm$  SD,  $n = 5-6$ ). **(C)** Percentage of weight change comparing naïve *Cyb5R3* SPC-KO mice in the different treatment arms. (Data point is mean  $\pm$  SD,  $n = 5-6$ ). **(D)** Relative expression changes of fibrotic markers *Col1a1* and *Col3a1* mRNA levels after treatments in uninjured *Cyb5R3* fl/fl and *Cyb5R3* SPC-KO mice. (Min-to-max with median,  $n = 5-6$ /group). **(E)** Change in transcript levels of *Tgfb1* and *Spp1* after treatments in *Cyb5R3* fl/fl and *Cyb5R3* SPC-KO uninjured mice. (Min-to-max with median,  $n = 5-6$ /group). **(F)** Relative expression changes of *Il6* mRNA levels after treatments in uninjured *Cyb5R3* fl/fl and *Cyb5R3* SPC-KO mice. (Min-to-max with median,  $n = 5-6$ /group). **(G)** Change in transcript levels of *Cdkn1a* and *Cdkn2a* after treatments in *Cyb5R3* fl/fl and *Cyb5R3* SPC-KO uninjured mice. (Min-to-max with median,  $n = 5-6$ /group). Statistical analysis was performed using 2-way ANOVA with multiple comparison test (B, D-G) and 1-way repeated measures ANOVA (C); as indicated: \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ ; \*\*\*\* $p < 0.0001$ ; n.s., non-significant.



**Supplemental Figure 11. Therapeutic intervention with sGC agonists ameliorates fibrotic and senescence outcomes in *Cyb5r3* SPC-KO mice after injury at 28 days.**

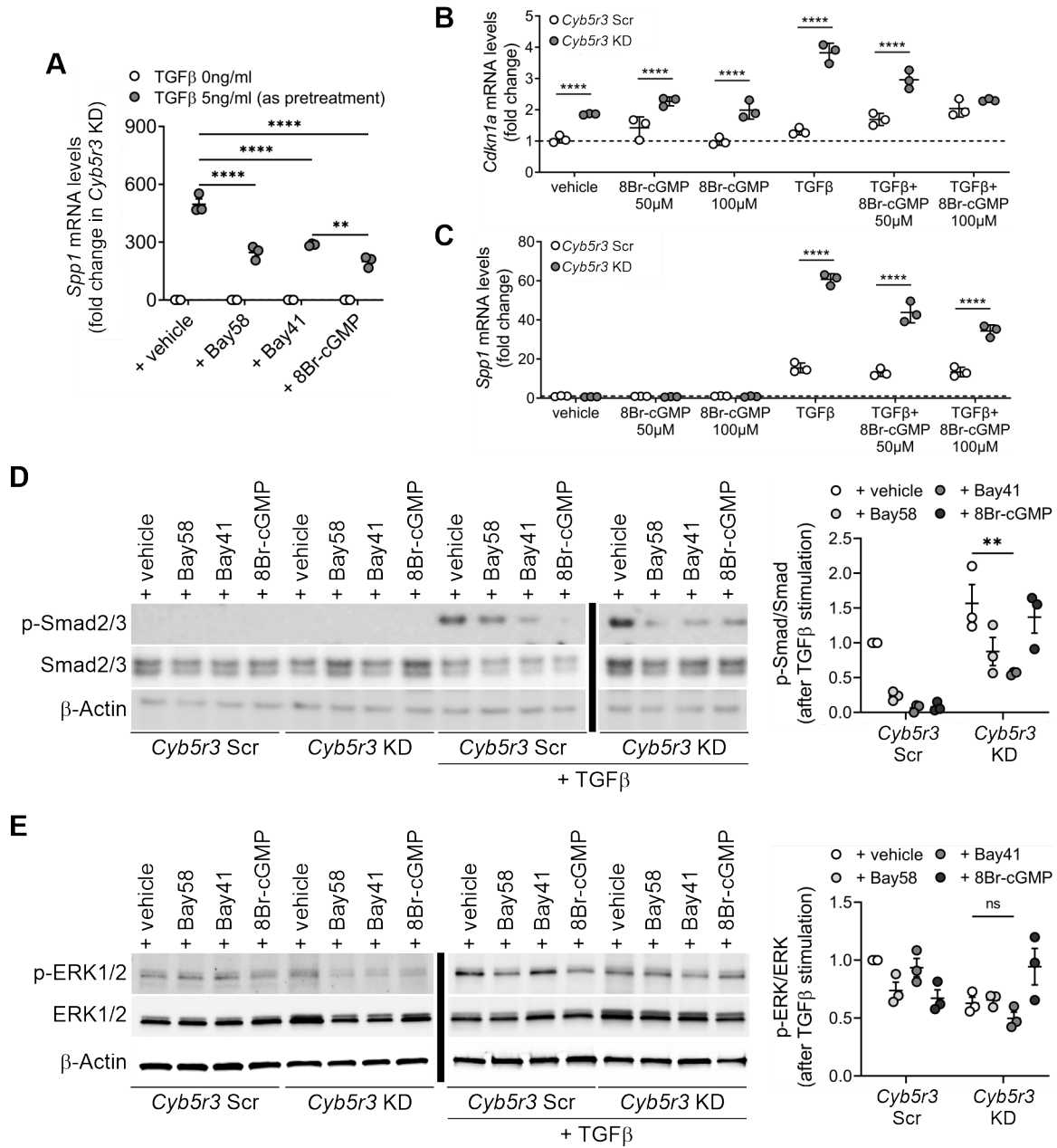
(A) Representative Masson trichrome staining in lung sections from *Cyb5r3* fl/fl and *Cyb5r3* SPC-KO mice at day 28 post MHV68 infection with different interventions (Placebo, sGC stimulator BAY 41-8543 or sGC activator BAY 54-6544). Scale bars: 200  $\mu$ m. ( $n = 12-4$ /group) (B) Weight loss data comparing treatments in the presence or

absence of CYB5R3 in the AECII. (Data point is mean  $\pm$  SD,  $n = 4-12$ ). (C) Change in transcript levels of *Cdkn1a* and *Cdkn2a* after treatments in *Cyb5R3* fl/fl and *Cyb5R3* SPC-KO MHV68-infected mice. (Min-to-max with median,  $n = 4-12$ /group). Statistical analysis was performed using 1-way repeated measure ANOVA (B), and 2-way ANOVA with multiple comparison test (C); as indicated: \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ ; \*\*\*\* $p < 0.0001$ ; n.s., non-significant.



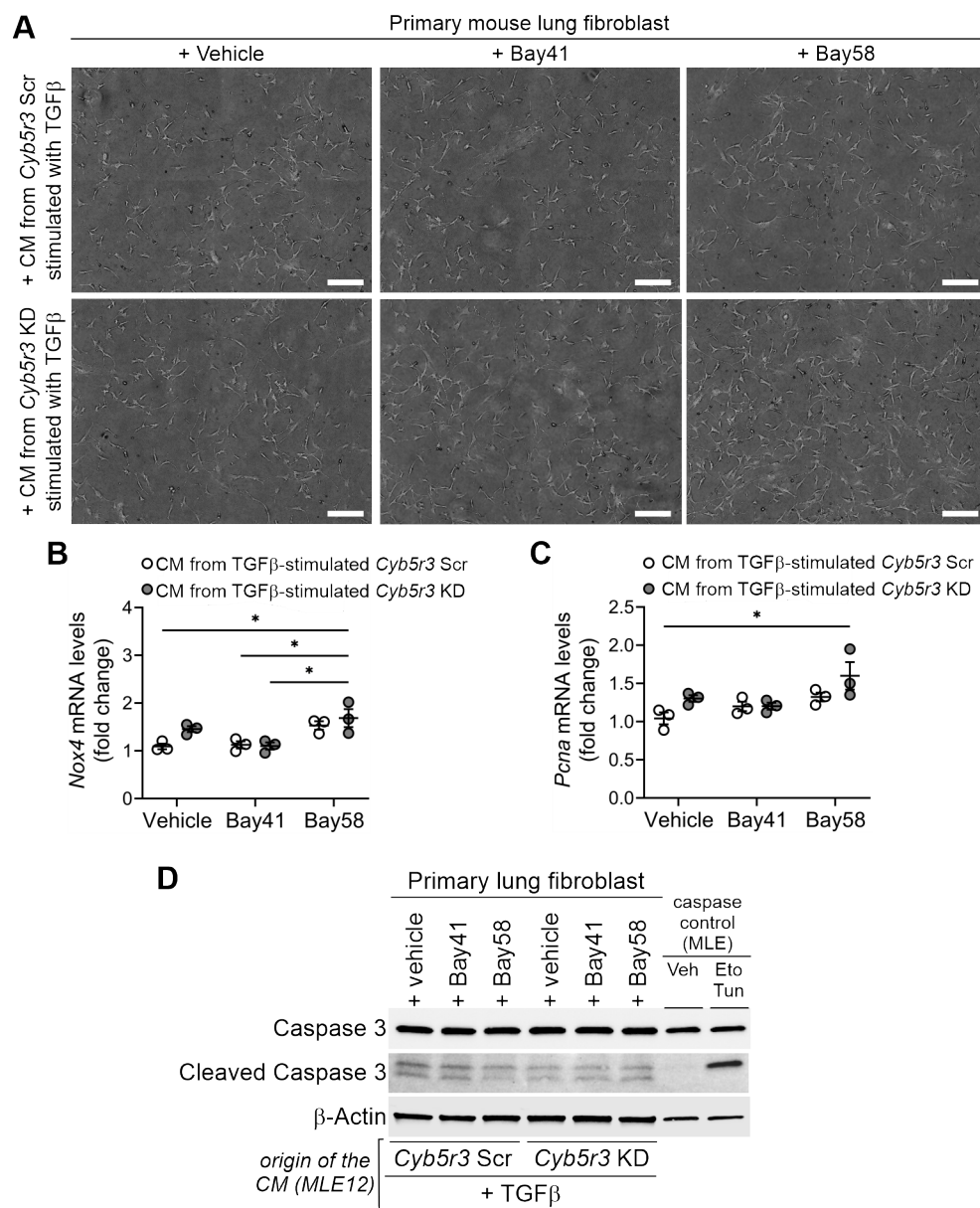
**Supplemental Figure 12. CYB5R3 deficiency is associated with oxidative stress and a pro-fibrotic phenotype.** Transcript levels of *Cyb5r3* (A), *Serpine1* (B) and *Fn1* (C) upon stimulation with TGF-β (8h stimulation, 48h wash-out), in *Cyb5r3* Scr and *Cyb5r3* KD MLE12 cells. (Min-to-max with median,  $n = 3/\text{group}$ ). (D) Levels of secreted active and total TGF-β1 in the media of *Cyb5r3* Scr and *Cyb5r3* KD MLE12 cells after 48h in culture (Individual data with mean ± SEM,  $n = 3/\text{group}$ ). (E) Levels of secreted osteopontin in the media of *Cyb5r3* Scr and *Cyb5r3* KD MLE12 cells after 48h in culture (Min-to-max with median,  $n = 3/\text{group}$ ). Statistical analysis was performed using 2-way ANOVA with multiple comparison test (A-C, E) and 2-tailed Student's t test (D); versus PBS: \*\* $p < 0.01$ , \*\*\* $p < 0.001$ , \*\*\*\* $p < 0.0001$ ; as indicated: #### $p < 0.001$ , ##### $p < 0.0001$ ; n.s., non-significant.





**Supplemental Figure 13. CYB5R3 modulates expression of TGF-β1-target genes via sGC-dependent pathways.** (A) Diminution of the TGFβ-mediated expression of *Spp1* in *Cyb5r3* KD MLE12 cells also if the TGF-β stimulation is performed as a pre-treatment (administered 30 min before the sGC agonist or the 8Br-cGMP). (Individual data with mean ± SEM,  $n = 3/\text{group}$ ). The action of cGMP over the expression of the TGF-β1-target genes *Cdkn1a* (B) and *Spp1* (C) is dose dependent in *Cyb5r3* Scr and *Cyb5r3* KD MLE12

cells. (TGF- $\beta$ 1 stimulation: 5ng/ml for 48h; all treatments administered simultaneously) (Individual data with mean  $\pm$  SEM,  $n = 3$ /group). **(D)** Representative immunoblot and quantification of the phosphorylation of Smad2/3 in *Cyb5r3* Scr and *Cyb5r3* KD MLE12 cells stimulated with 5 ng/ml of TGF- $\beta$ 1 for 30min in the presence of different sGC agonists (pre-treatments for 30min before stimulation). (Individual data with mean  $\pm$  SEM,  $n = 3$ /group). (Black bar separate data from two separate blots). **(E)** Representative immunoblot and quantification of the phosphorylation of ERK1/2 in *Cyb5r3* Scr and *Cyb5r3* KD MLE12 cells stimulated with 5 ng/ml of TGF- $\beta$ 1 for 30min in the presence of different sGC agonists (pre-treatments for 30min before stimulation). (Individual data with mean  $\pm$  SEM,  $n = 3$ /group). (Black bar separate data from two separate blots). Statistical analysis was performed using 1-way ANOVA with multiple comparison test (A-C), and 2-way ANOVA with multiple comparison test (D-E); as indicated: \* $p < 0.05$ ; \*\* $p < 0.01$ ; \*\*\* $p < 0.0001$ ; \*\*\*\* $p < 0.00001$ .



**Supplemental Figure 14. Effects of sGC agonists on primary mouse lung fibroblasts in culture.** (A) Representative images of murine primary lung fibroblasts cultured for 48h in the presence of conditioned media (CM) derived from *Cyb5r3* Scr or *Cyb5r3* KD MLE12 cells previously stimulated with TGF- $\beta$  in the presence/absence of different sGC agonists (BAY 58-2667 1  $\mu$ M or BAY 41-2272 1  $\mu$ M). Fibroblasts were preincubated in vehicle (0.01% DMSO) or sGC agonist for 30 min before receiving the CM (in a 1:1 ratio, CM to fresh fibroblast culture media). To generate the CM media, at

24h post adenovirus-infection, *Cyb5r3* Scr or *Cyb5r3* KD MLE12 cells received recombinant TGF- $\beta$ 1 or PBS at 10 ng/ml for 8 hours, then (after extensive washes) cells were cultured in fresh TGF- $\beta$ 1-free culture media for 24 hours and media were harvested. Scale bars: 275  $\mu$ m. ( $n$  = 3/condition). **(B)** Levels of *Nox4* and *Pcna* mRNA transcript from primary fibroblast cultured in conditioned media derived from *Cyb5r3* Scr or *Cyb5r3* KD MLE12 cells previously stimulated with TGF $\beta$  in the presence of sGC modulators as described above. (Individual data with mean  $\pm$  SEM,  $n$  = 3/group). **(C)** Representative immunoblot detecting changes in levels of cleaved caspase 3 in the same samples. ( $n$  = 3). Statistical analysis was performed using 2-way ANOVA with multiple comparison test (B-C); as indicated: \* $p$ <0.05.

**Supplemental Table S1.** Demographic characteristic of the patients cohort

| <i>NAD<sup>+</sup>/NADH cohort</i> |                      |                    |                   |
|------------------------------------|----------------------|--------------------|-------------------|
|                                    | <b>Donor (Young)</b> | <b>Donor (Old)</b> | <b>IPF</b>        |
| <b>Subjects</b>                    | 5                    | 5                  | 5                 |
| <b>Age</b>                         | 27±5<br>(20 – 32)    | 72±7<br>(65 – 80)  | 68±3<br>(64 – 74) |
| <b>Female</b>                      | 2 (40%)              | 2 (40%)            | 2 (40%)           |
| <b>Male</b>                        | 3 (60%)              | 3 (60%)            | 3 (60%)           |

| <i>Cyb5R3 immunofluorescence cohort</i> |                   |                   |
|-----------------------------------------|-------------------|-------------------|
|                                         | <b>Donor</b>      | <b>IPF</b>        |
| <b>Subjects</b>                         | 3                 | 3                 |
| <b>Age</b>                              | 66±2<br>(63 – 68) | 60±6<br>(54 – 68) |
| <b>Female</b>                           | 1 (33%)           | 1 (33%)           |
| <b>Male</b>                             | 2 (67%)           | 2 (67%)           |

| <i>Human lung Fibroblast origin cohort</i> |                      |                    |                   |
|--------------------------------------------|----------------------|--------------------|-------------------|
|                                            | <b>Donor (Young)</b> | <b>Donor (Old)</b> | <b>IPF</b>        |
| <b>Subjects</b>                            | 3                    | 3                  | 3                 |
| <b>Age</b>                                 | 24±3<br>(22 – 27)    | 66±7<br>(62 – 74)  | 60±3<br>(58 – 63) |
| <b>Female</b>                              | 1 (33%)              | 2 (66%)            | 2 (66%)           |
| <b>Male</b>                                | 2 (66%)              | 1 (33%)            | 1 (33%)           |

**Supplemental Table 2.** List of PrimeTime® primer assays (Integrated DNA Technologies)

| <b>Gene</b>   | <b>Assay ID</b>       |
|---------------|-----------------------|
| <i>Rn18s</i>  | Mm.PT45.122532.g      |
| <i>Tgfb1</i>  | Mm.PT.58.11254750     |
| <i>Sftpc</i>  | Mm.PT.58.9922071      |
| <i>Cdkn1a</i> | Mm.PT.51.17125846     |
| <i>Cdkn2a</i> | Mm.PT.51.5632963      |
| <i>Cyb5r3</i> | Mm.PT.58.10895816     |
| <i>Il6</i>    | Mm.PT.49a.11799101.g  |
| <i>Col1a1</i> | Mm.PT.47.12668954     |
| <i>Col3a1</i> | Mm.PT.58.32580981     |
| <i>Fn1</i>    | Mm.PT.58.8135568      |
| <i>Spp1</i>   | Mm.PT.58.43709208     |
| <i>Timp1</i>  | Mm.PT.53A.30682575    |
| <i>Timp2</i>  | Mm.PT.53a.31075226    |
| <i>Timp3</i>  | Mm.PT.53a.5548479     |
| <i>Mmp2</i>   | Mm.PT.49a.10834743    |
| <i>Mmp3</i>   | Mm.PT.53a.10373662    |
| <i>Mmp8</i>   | Mm.PT.53a.11894446    |
| <i>Mmp9</i>   | Mm.PT.47.7474177.g    |
| <i>Mmp12</i>  | Mm.PT.47.17468164     |
| <i>Mmp13</i>  | Mm.PT.53a.9491926     |
| <i>Mmp14</i>  | Mm.PT.53a.5295525     |
| <i>Mmp19</i>  | Mm.PT.53a.6013546     |
| <i>Ptgs1</i>  | Mm.PT.58.13984299     |
| <i>Ptgs2</i>  | Mm.PT.58.9154407      |
| <i>Il1b</i>   | Mm.PT.49a.17212823    |
| <i>Il10</i>   | Mm.PT.49a.11509489.gs |

|                 |                      |
|-----------------|----------------------|
| <i>Ifng</i>     | Mm.PT.58.41769240    |
| <i>Fgf2</i>     | Mm.PT.56a.5129235    |
| <i>Gucy1b3</i>  | Mm.PT.58.14181337    |
| <i>Gdf15</i>    | Mm.PT.58.13112185    |
| <i>Cybs</i>     | Mm.PT.49a.10814950.g |
| <i>Ppara</i>    | Mm.PT.49a.9374886    |
| <i>Serpine1</i> | Mm.PT.58.6413525     |
| <i>Tgfb2</i>    | Mm.PT.58.14105470    |
| <i>Tgfb3</i>    | Mm.PT.58.6019015     |