Supplemental Information

Supplemental Materials and Methods: Generation of C57BL/6 *Nfe2l2* $^{flox/flox}$ mice. C57BL/6 *Nfe2l2* $^{flox/flox}$ mice were generated by inGenious Targeting Laboratory using a targeting vector that inserted a loxP/FRT flanked Neo cassette on the 3' side of exon 5 and a single loxP site on the 5' side of exon 4. The target region was 2843 bps and included exons 4 and 5. The linearized targeting construct was electroporated into ES cells. After selection with G418 antibiotic, surviving clones were expanded for PCR analysis to identify recombinant ES clones and then reconfirmed using Southern blotting. Recombinant ES clones were then injected into recipient female mice. The resulting chimera mice were crossed to FLP mice to remove the Neo cassette. These mice were backcrossed to C57BL/6j mice for more than 6 generations. We chose to delete exons 4 and 5 in the *Nfe2l2* $^{flox/flox}$ mice in order to generate an Nrf2 defect that was similar to that in the *Nfe2l2* $^{-/-}$ mice [25].

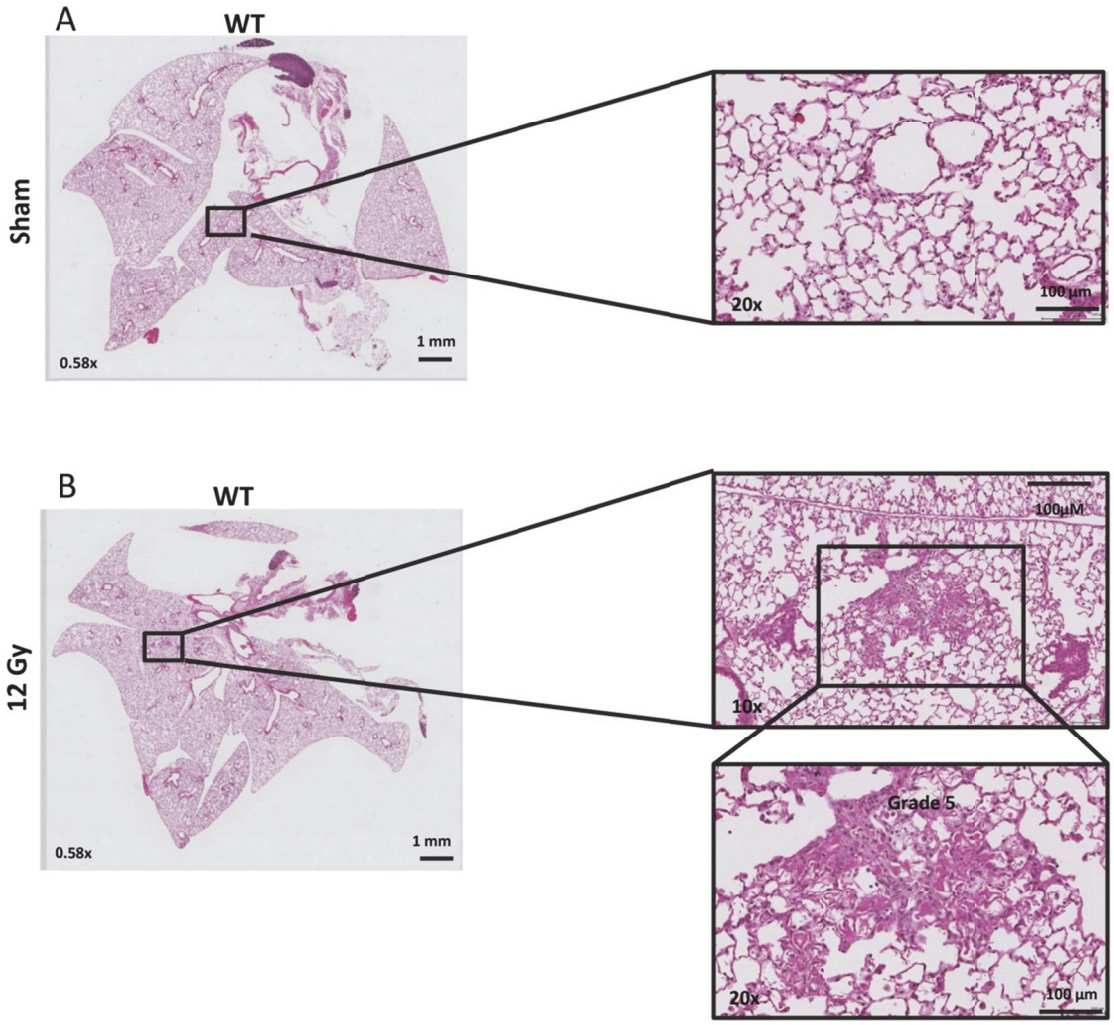


Fig S1: Wide field whole slide scanning microscopy was used to image H&E staining. The thorax of male wild type mice was administered 0 (A) or 12 Gy (B) and the mice allowed to recover for 250 days. H&E stained lung sections obtained 250 days after sham (A) or irradiation (12Gy, B) treatment. A) The section illustrates sham treated lung imaged at 0.58x and at 20x. B) The section illustrates tissue remodeling observed in irradiated lung. The degree of remodeling was quantified as described in the Materials and Methods section and in Supplemental Table S1.

Supplemental Table S1

Grade	Area of remodeling as a percent of Field Size
1	Normal lung
2	< 5%
3	> 5% to < 10%
4	> 10% to < 20%
5	> 20% to < 30%
6	> 30% to < 40%
7	> 40% to < 50%
8	> 50%

The area occupied by tissue remodeling within a H&E stained slide was quantified in μm^2 and expressed relative to the area of the entire field. A scale of 1-8 was employed (26).

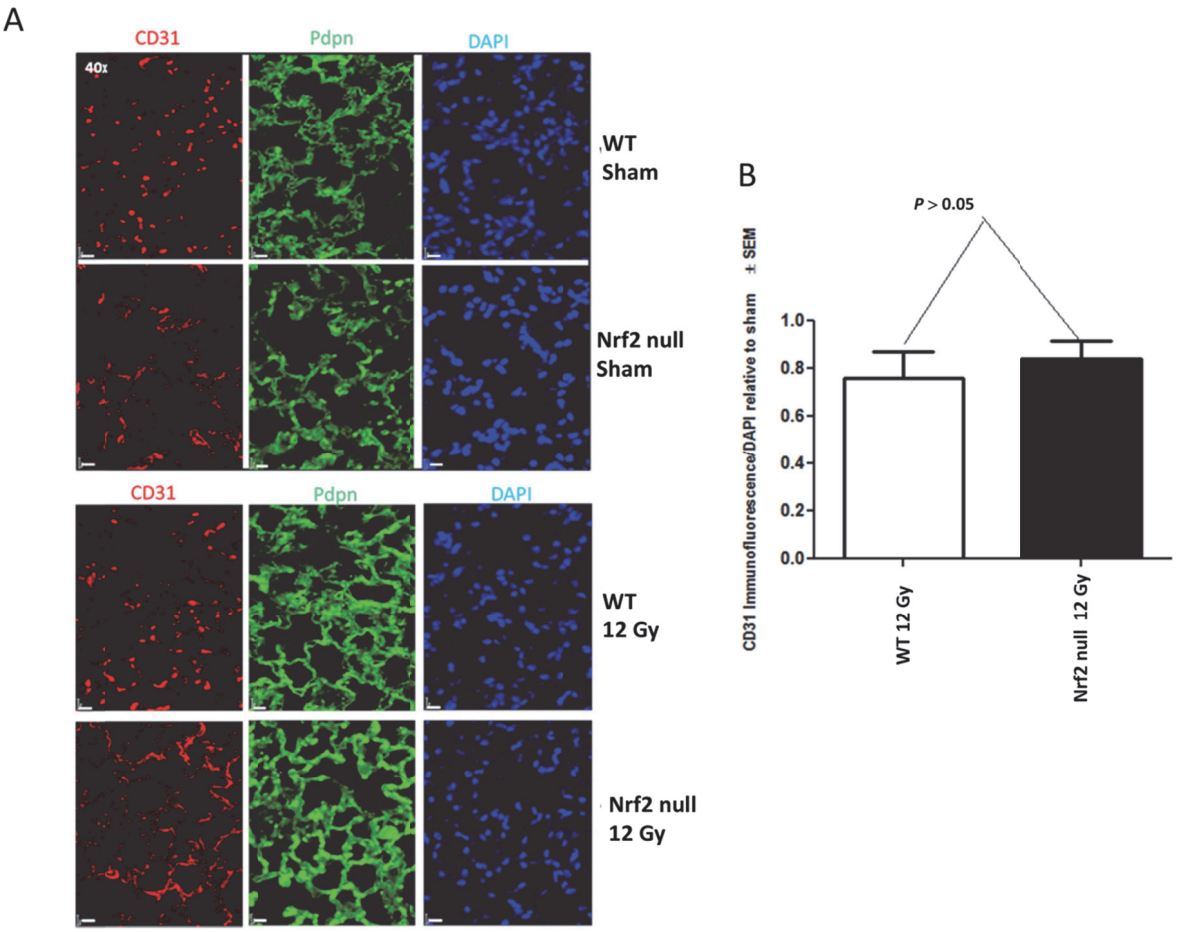
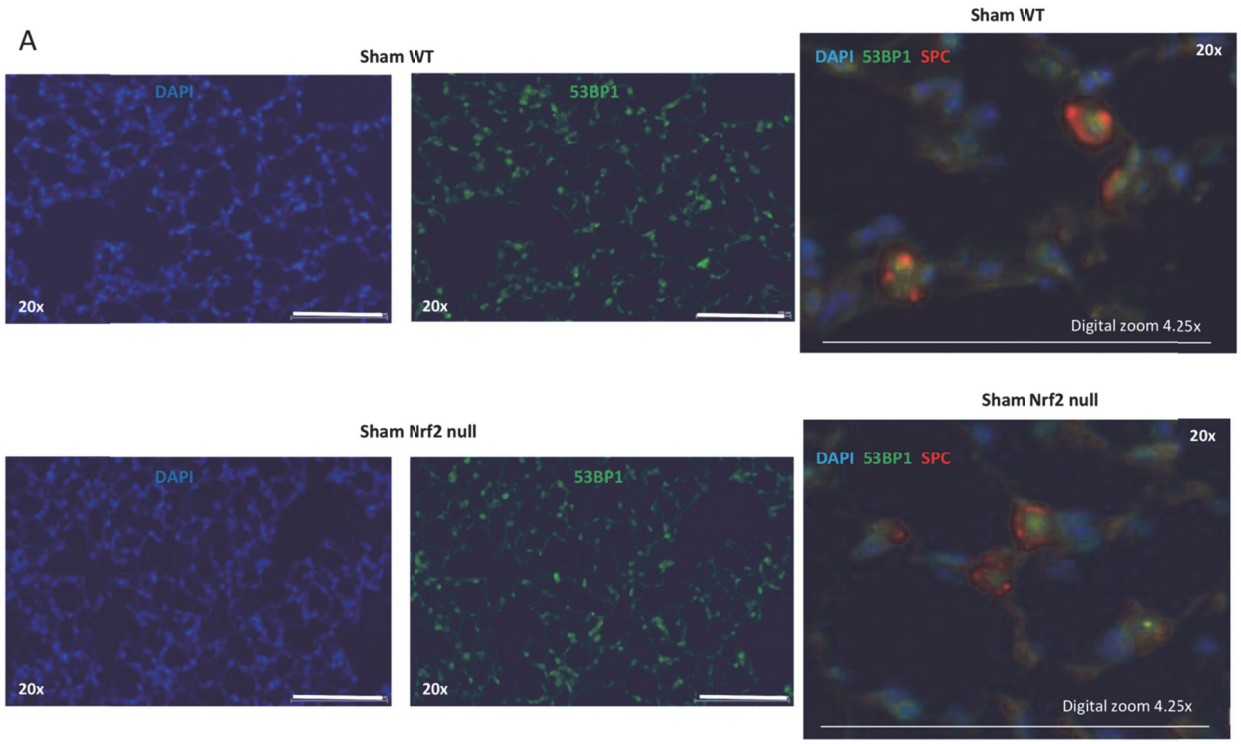
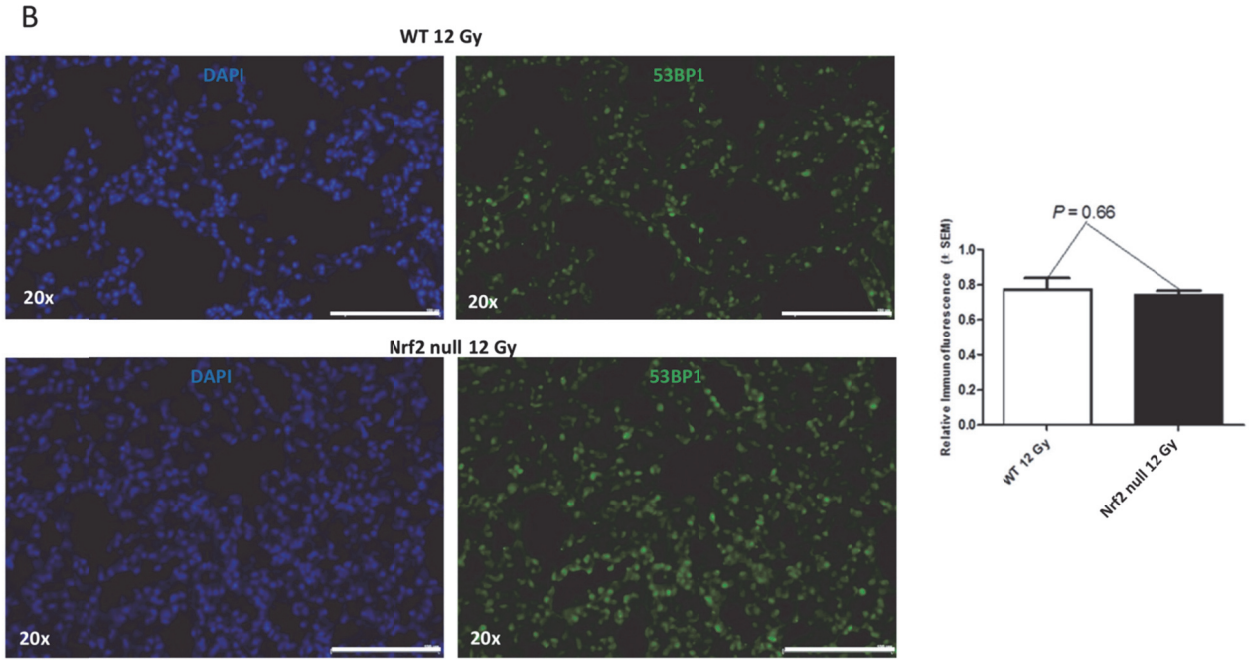


Fig S2: Loss of Nrf2 does not potentiate endothelial cell loss following irradiation. The thorax of wild type and Nrf2 null mice was administered 12 Gy and the mice were allowed to recover for 250 days. Wide field whole slide scanning microscopy was used to quantify CD31 immunofluorescence in Pdpn marked alveoli. A) Representative images of CD31 and Pdpn immunostaining. B) Quantification of CD31 immunofluorescent cells per field relative to sham treatment, corrected for DAPI staining. N = 10 mice, 99 fields. 40x, White bar = 10 μm


A
Sham WT
DAPI
20x
53BP1
20x
Sham WT
DAPI 53BP1 SPC
20x
Digital zoom 4.25x
Sham Nrf2 null
DAPI
20x
53BP1
20x
Sham Nrf2 null
DAPI 53BP1 SPC
20x
Digital zoom 4.25x


B
WT 12 Gy
DAPI
20x
53BP1
20x
Nrf2 null 12 Gy
DAPI
20x
53BP1
20x
P = 0.66
Relative Immunofluorescence (± SEM)
1.0
0.8
0.6
0.4
0.2
0.0
WT 12 Gy
Nrf2 null 12 Gy

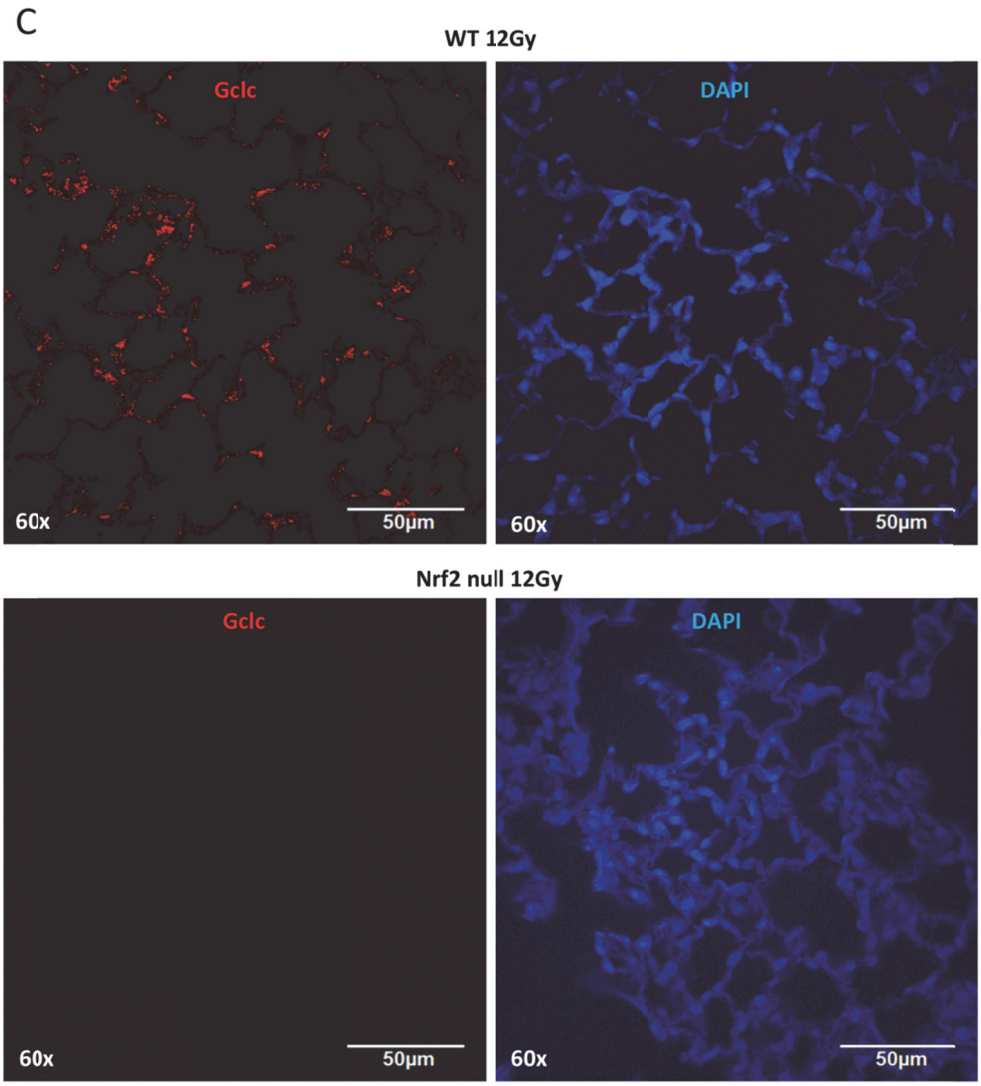


Fig S3: Expression of 53PB1 is not suppressed in sham-treated or irradiated (12 Gy) Nrf2 null mice. The thorax of wild type and Nrf2 null mice was administered 0 or 12 Gy and the mice were allowed to recover for 250 days. A & B) Wide field whole slide scanning microscopy was used to quantify Spc immunofluorescent (red) and 53BP1 immunofluorescent (green) cells per field, corrected for DAPI staining. White bar = 100 µm. 20x. C) Confocal microscopy was used to image Gclc immunofluorescence (red) and DAPI staining. White Bar = 50 µm. 60x.

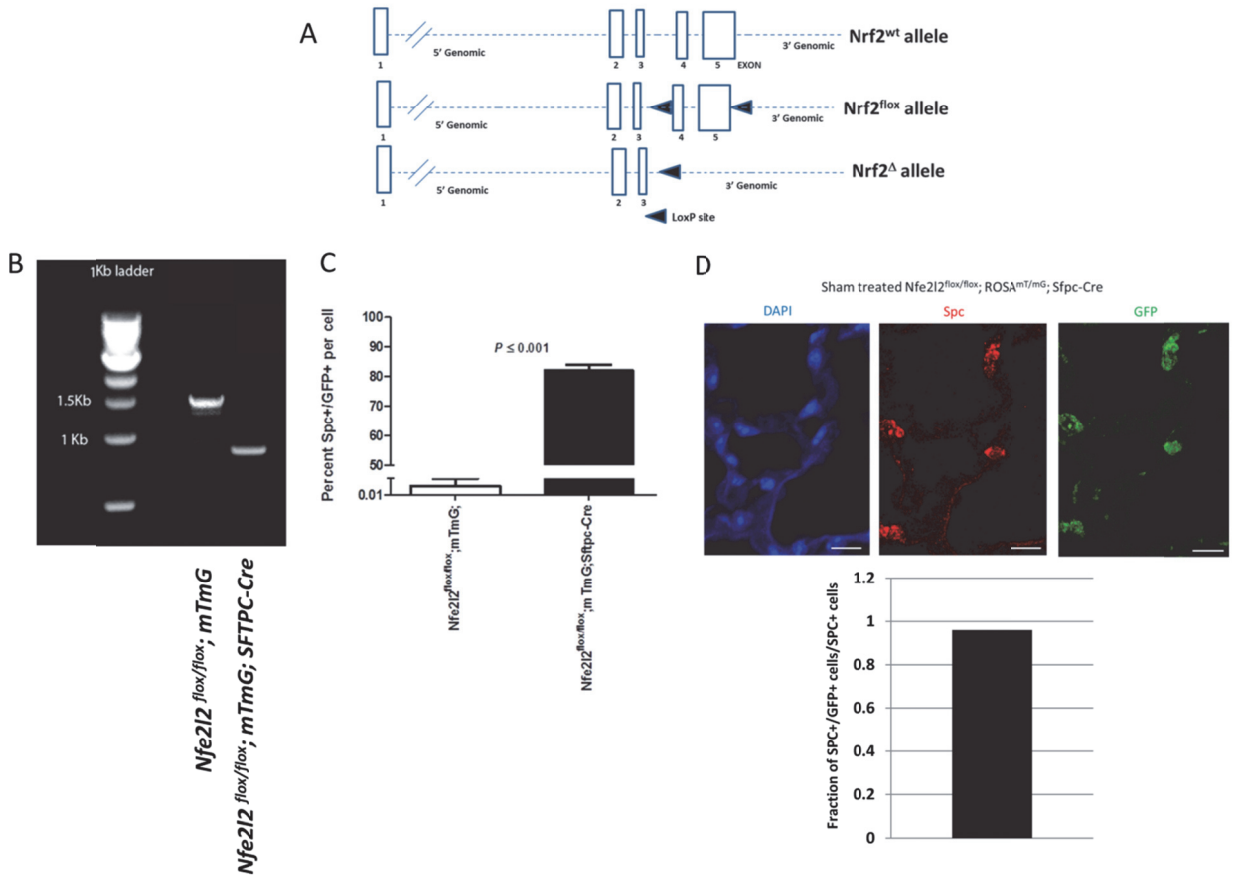


Fig S4: Conditional disruption of the *Nfe2l2* allelle. A) Schematic of the *Nfe2l2* allele illustrating the location of the loxP sites. B) PCR of genomic DNA obtained from the lungs of *Nfe2l2*$^{flox/flox}$; *ROSA*^{mTmG} and *Nfe2l2*$^{flox/flox}$;*ROSA*^{mTmG}; *SFTPC-Cre mice*. The bands illustrate the presence of the exons 4 and 5 in *Nfe2l2*$^{flox/flox}$; *ROSA*^{mTmG} mice and loss of exons 4 and 5 in *Nfe2l2*$^{flox/flox}$;*ROSA*^{mTmG}; *Sftpc-Cre* mice. C) . Single cell suspensions were made from the lungs of *Nfe2l2*$^{wt/wt}$; ROSA$^{mT/mG}$ and *Nfe2l2*$^{flox/flox}$; ROSA$^{mT/mG}$;*SFTPC-Cre* mice. Flow cytometry was used to quantify Spc immunofluorescence, tdTomato red and GFP fluoresence per cell. Greater than 98% of Spc positive cells obtained from *Nfe2l2*$^{wt/wt}$; ROSA$^{mT/mG}$ mice co-expressed dtTomato red. 82 ± 2 (SD) % of Spc positive cells obtained from *Nfe2l2*$^{flox/flox}$; ROSA$^{mT/mG}$;*SFTPC-Cre* mice were also positive for GFP ($P < 0.001$) indicating that the majority of Type 2 cells underwent Cre-mediated recombination. D) 60x confocal image with a 200x digital zoom of a lung section obtained from a sham treated *Nfe2l2*$^{flox/flox}$;*ROSA*^{mTmG}; *Sftpc-Cre* mouse. The image illustrates Spc immunofluoresent (false red, Alexa 568 nm) cells also express GFP fluoresence, and DAPI staining. In total 105 Spc positive DAPI stained cells were counted. 103 or 0.98 also expressed GFP. White bar = 10 µm.