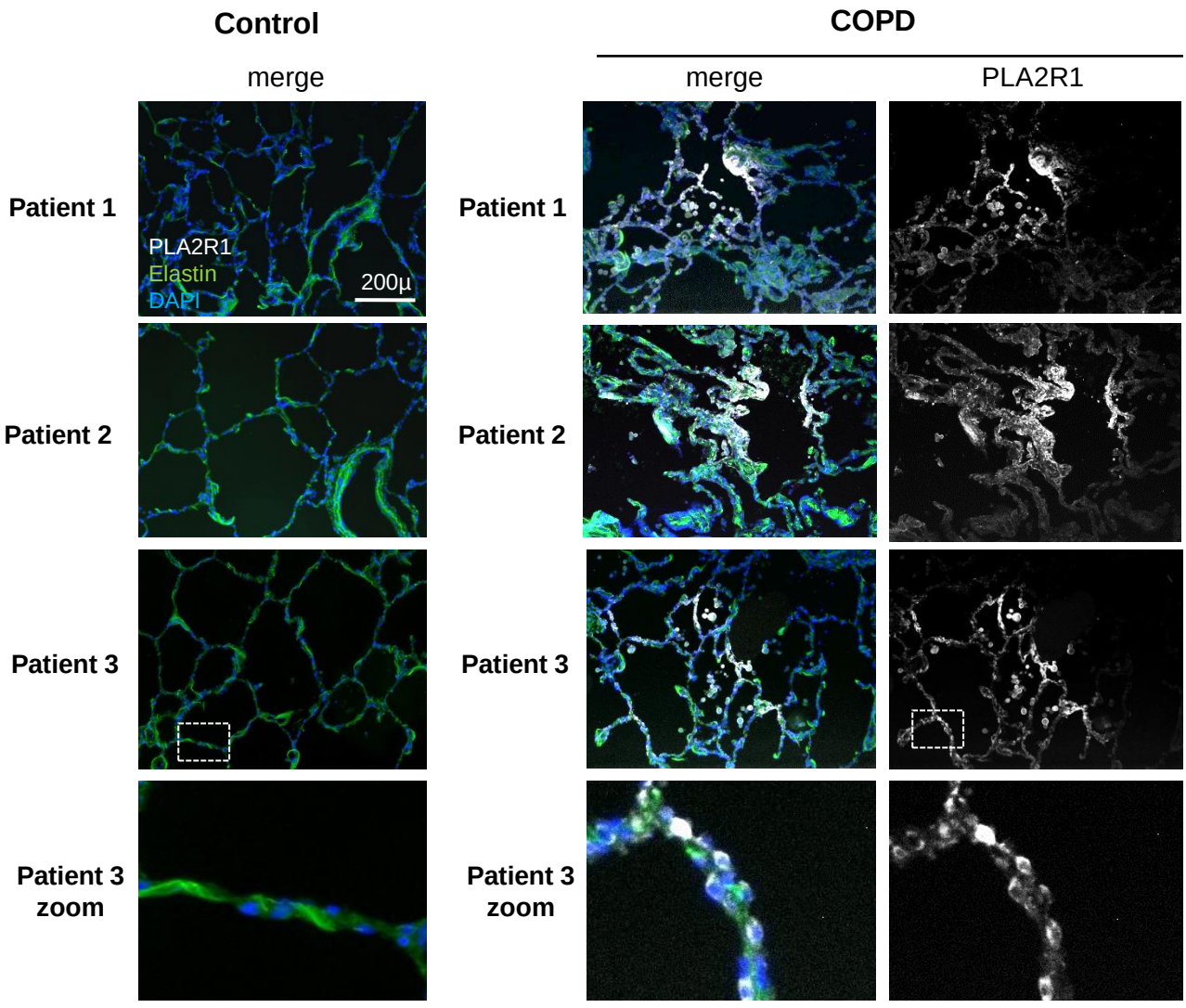
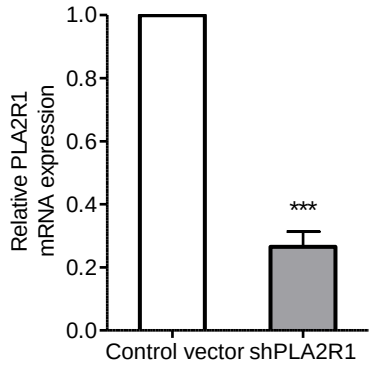
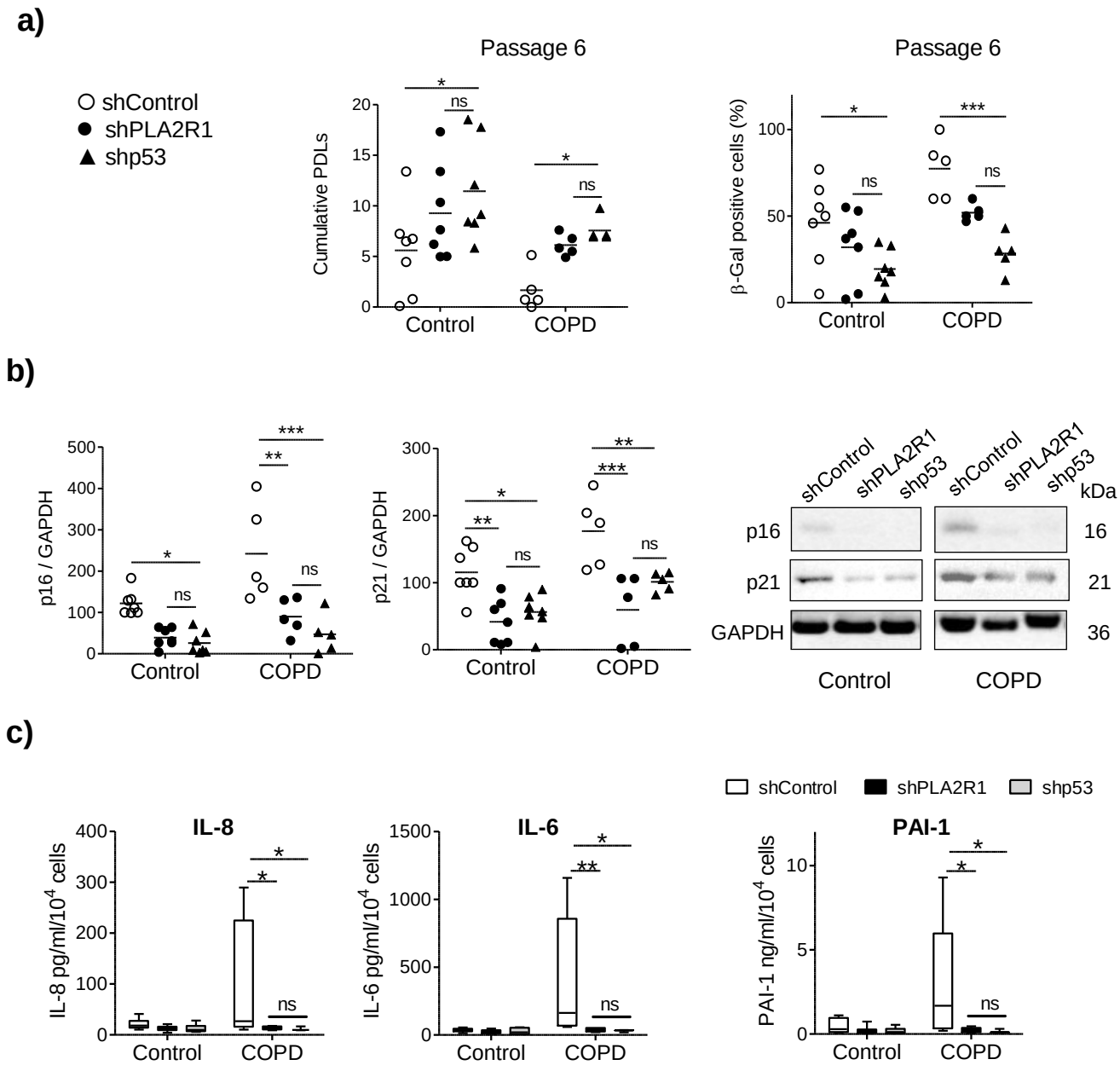


Supplemental Figure 1
Distribution of PLA2R1 immunofluorescence activity in lungs from patients with COPD and controls
Representative micrographs of lung tissue from 3 patients with COPD and 3 controls showing PLA2R1 expression (white), and merge with elastin autofluorescence (green) and nuclear DAPI staining (blue). The zoom area is indicated by a square.



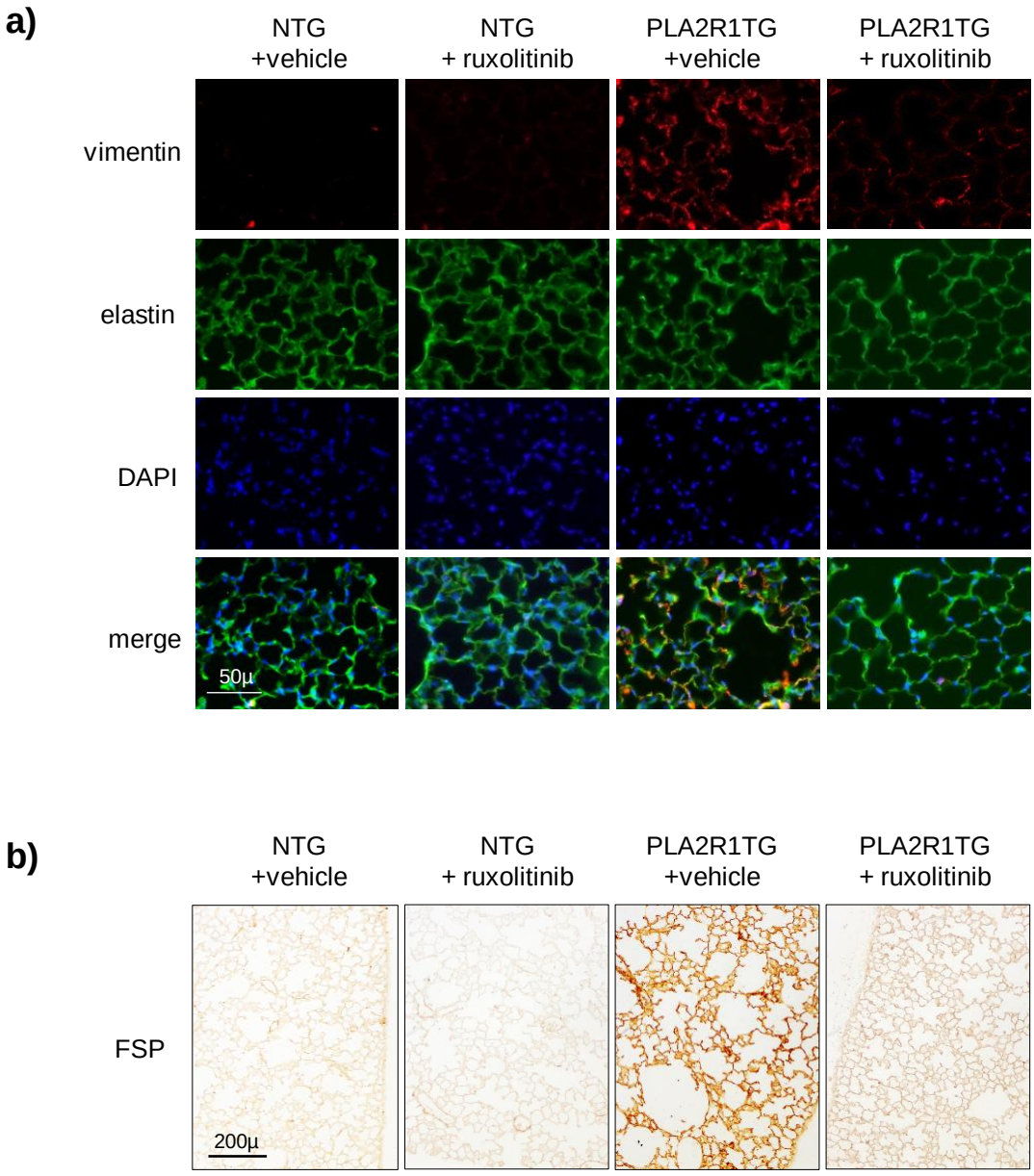
S**upplemental Figure 2:** *PLA2R1* mRNA levels measured in cells stably infected with the sh*PLA2R1*-encoding retroviral vector, compared to cells infected with the control vector. ****P*<0.001 for comparison between groups, Student's *t*-test



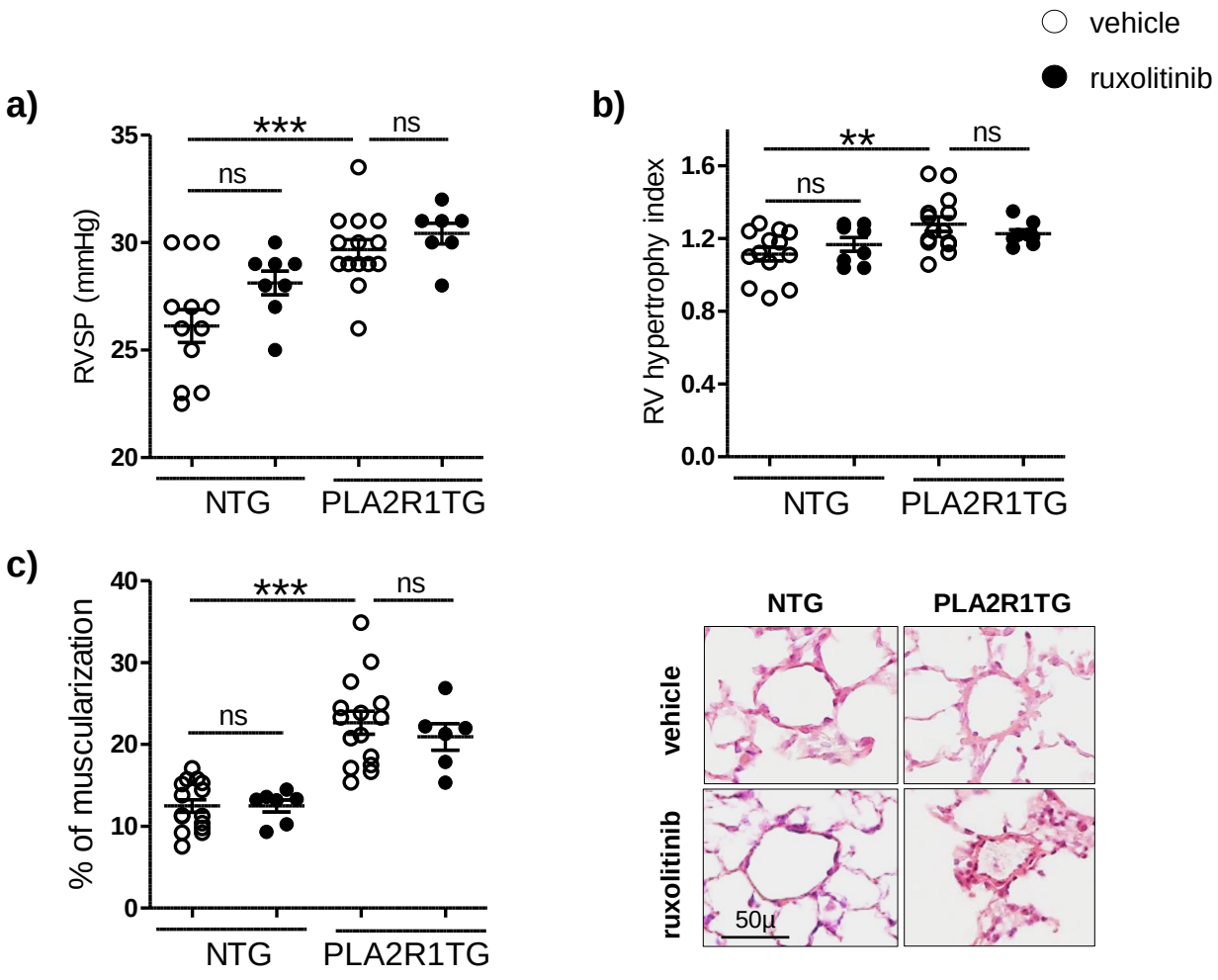
Supplemental Figure 3

Comparison between inactivation of *PLA2R1* and *p53* in cells from patients with COPD and controls

Cells from patients with COPD (n=5) and controls (n=5) were infected either with a retroviral vector encoding an shRNA that targeted *PLA2R1* (sh*PLA2R1*) or *p53* (sh*p53*) or with a control vector encoding a scramble sequence (shControl). The cells were then subjected to successive passages. **(a, b)** Graphs showing cumulative numbers of PDLs, percentage of β-Gal-positive cells, and p16 and p21 protein levels as assessed by Western blotting, all determined at passage 6 are shown as individual values with the mean. Representative immunoblots are shown on the right. **P*<0.05, ***P*<0.01, ****P*<0.001 vs. shControl, two-way ANOVA with Bonferroni's multiple comparisons test. **(c)** Protein levels of IL-8, IL-6, and PAI-1 in PA-SMC-conditioned media at passage 6. Data are shown as median (interquartile range) of 5 values per group. Bars represent extreme values. There were no significant differences between values recorded in cells treated with the sh*PLA2R1* or the sh*p53* vectors. **P*<0.05, ***P*<0.01 vs. shControl one-tailed Mann Whitney test.

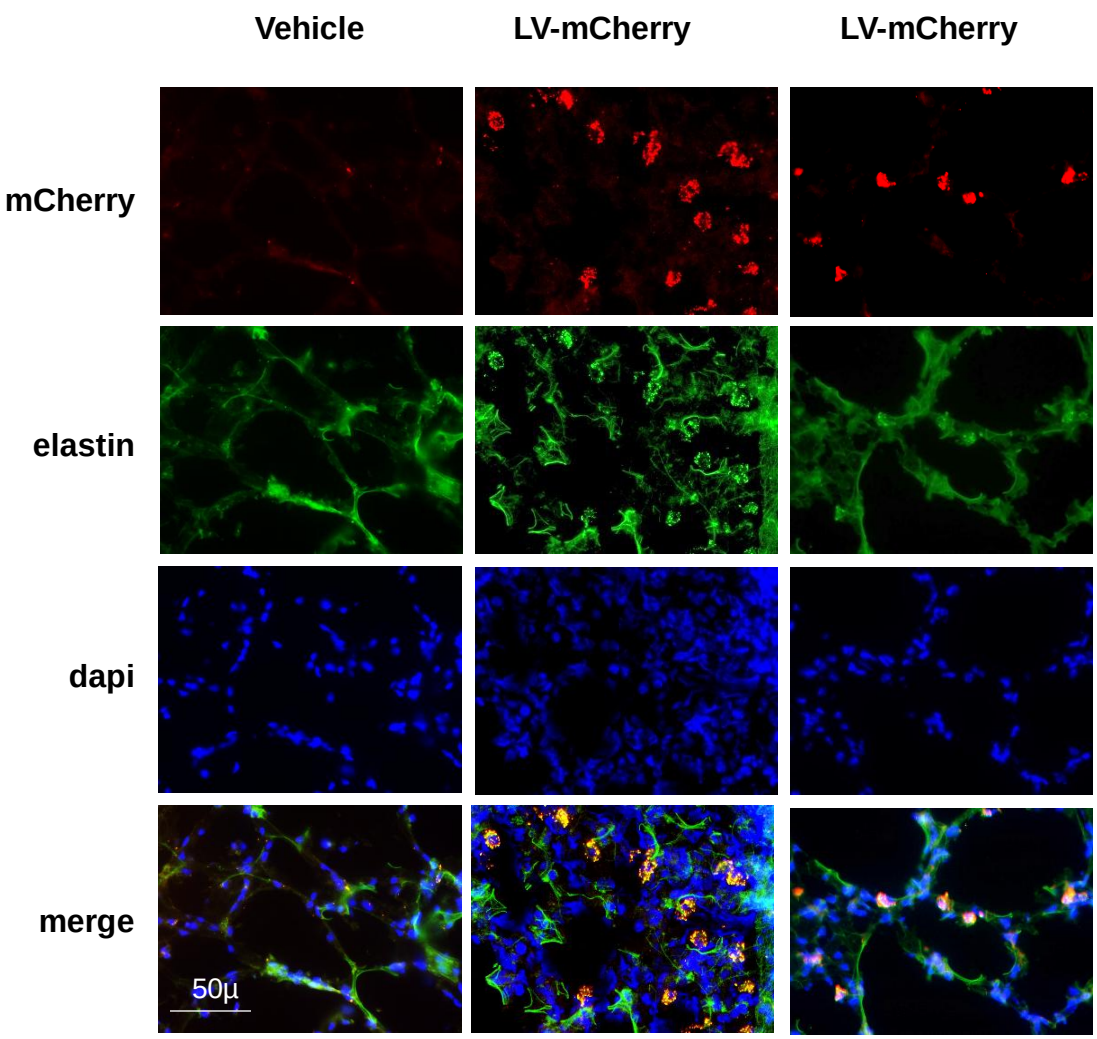


Supplemental Figure 4
Lung vimentin and fibroblast-specific protein (FSP) immunostaining in *PLA2R1*TG mice and littermate controls subjected to 15 days of treatment with ruxolitinib or vehicle.
(a) Representative micrographs showing lung sections stained for vimentin (red), a lung alveolar fibroblast marker, in *PLA2R1*-TG and control mice treated with ruxolitinib or vehicle. Elastin autofluorescence (green); the nuclei were stained with DAPI (blue). **(b)** Representative micrographs showing lung sections stained for fibroblast-specific protein (FSP, brown), a lung alveolar fibroblast marker, in the same groups of mice.

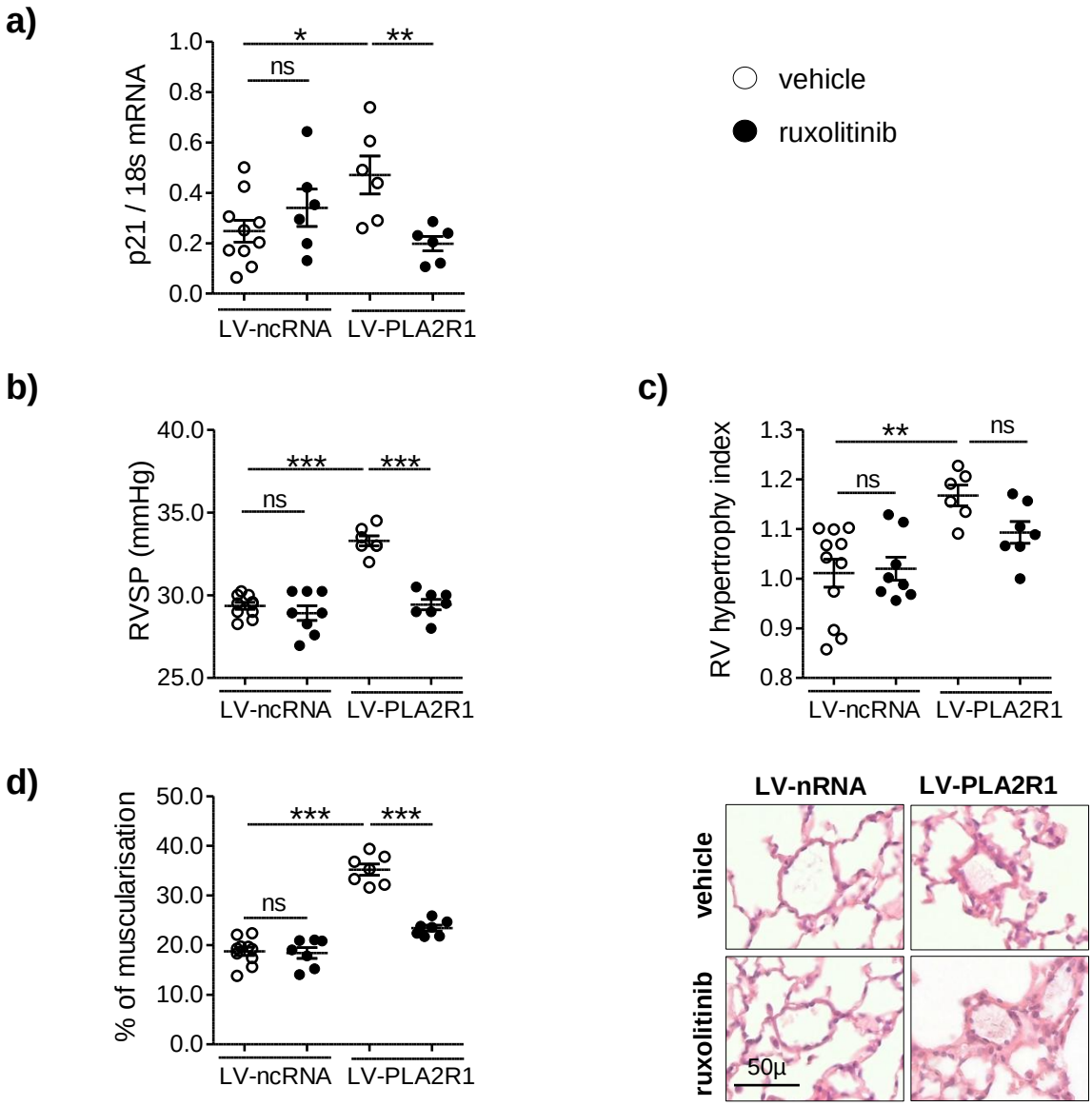


Supplemental Figure 5. **Pulmonary hemodynamic parameters in *PLA2R1*TG and littermate control (NTG) mice subjected to 15 days of treatment with ruxolitinib or vehicle**

(a) Right ventricular systolic pressure (RVSP) **(b)** Right ventricular hypertrophy index (Fulton's index) **(c)** Muscularization of pulmonary vessels (percent of muscularized vessels over the total number of pulmonary vessels) and representative images of pulmonary vessels. Graphs represent individual values with the mean±SEM. ***P*<0.01, ****P*<0.001 for comparisons between groups as indicated. Unpaired Student's *t*-test and two-way ANOVA with Bonferroni's multiple comparisons test.



Supplemental figure 6. Identification of lentivirus-transduced cells in the mouse lung.
A lentiviral vector encoding the mCherry gene under the control of the CMV promoter (LV-mCherry) was injected intratracheally to mice (109 TU/ml diluted in DPBS with 5% of Lipofectamine 2000) in comparison with vehicle (DPBS with 5% of Lipofectamine 2000). , Mice were sacrificed on day 9 post-infection, and lung cryosections were assessed by fluorescence microscopy for mCherry reporter gene expression (red). Green – elastin autofluorescence, nuclei were stained with DAPI (blue). Bar – 50µm.



Supplemental Figure 6

Pulmonary hemodynamic parameters in mice subjected to an intratracheal injection of a lentivirus encoding the mouse *Pla2r1* gene (LV-*PLA2R1*) and concomitantly treated with ruxolitinib

Mice treated with the LV-*PLA2R1* or a control vector (LV-ncRNA) and simultaneously treated with ruxolitinib (75 mg/kg/day) or vehicle were studied 30 days after the injection. **(a)** Lung mRNA level of p21 **(b)** Right ventricular systolic pressure (RVSP) **(c)** Right ventricular hypertrophy index (Fulton's index) **(d)** Muscularization of pulmonary vessels (percent of muscularized vessels over the total number of pulmonary vessels) and representative images of pulmonary vessels. Graphs represent individual values with the mean±SEM. ***P*<0.01, ****P*<0.001 for comparisons between groups as indicated. Student's *t*-test and two-way ANOVA with Bonferroni's multiple comparisons test.

Table S1

	Control		COPD	
	Mean	*sem*	Mean	*sem*
n	23		23	
Age, yr	65,17	±*2,60*	59,83	±1,27
FEV %	92,39	±*2,20*	77,78	±3,43
FVC%	96,23	±*2,98*	88,73	±5,10
FEV /FVC, %	82,74	±*1,89*	66,05	±1,13
Pack-years	25,74	±*4,76*	44,76	±5,23

Table S2

	Control		COPD	
	Mean	*sem*	Mean	*sem*
n	10		8	
Age, yr	62,72	±*4,27*	64,7	±*2,32*
FEV %	94,38	±*2,73*	69,78*	±*3,23*
FVC%	101,17	±*1,69*	80,67	±*5,97*
FEV/FVC,%	83,85	±*3,30*	62,2**	±*2,25*
Pack-years	19	±*5,39*	52,78*	±*6,67*

Supplemental Tables S1 and S2

Clinical features and pathological variables of patients with COPD and control smokers. Table S1 describes all patients and controls from whom lung samples were obtained. Cells were collected from a subset of 8 patients and 10 controls, whose characteristics are described in Table S2.

Abbreviations: FEV_1, forced expiratory volume in 1 second; FEV_1%, percentage of the predicted FEV_1 value; FVC, forced vital capacity; FVC%, percentage of the predicted FVC value.

Table S3 : TaqMan Gene Expression assays

Target Gene	Assay ID
hPLA2R1	Hs01073364_m1
mPLA2R1	Mm0476896_m1
p21	Mm04205640_g1
Tap1	Mm00443188_m1
SOCS1	Mm00782550_s1
Irf7	Mm00516793_g1
Col1a1	Mm00801666_g1
Col1a2	Mm00483888_m1
Col3a1	Mm00802300_m1
Acta2	Mm00725412_s1
Fibronectin	Mm01256744_m1

Reference Gene	Assay ID
hSF3A1	Hs01066327_m1
m18s	Mm03928990_g1