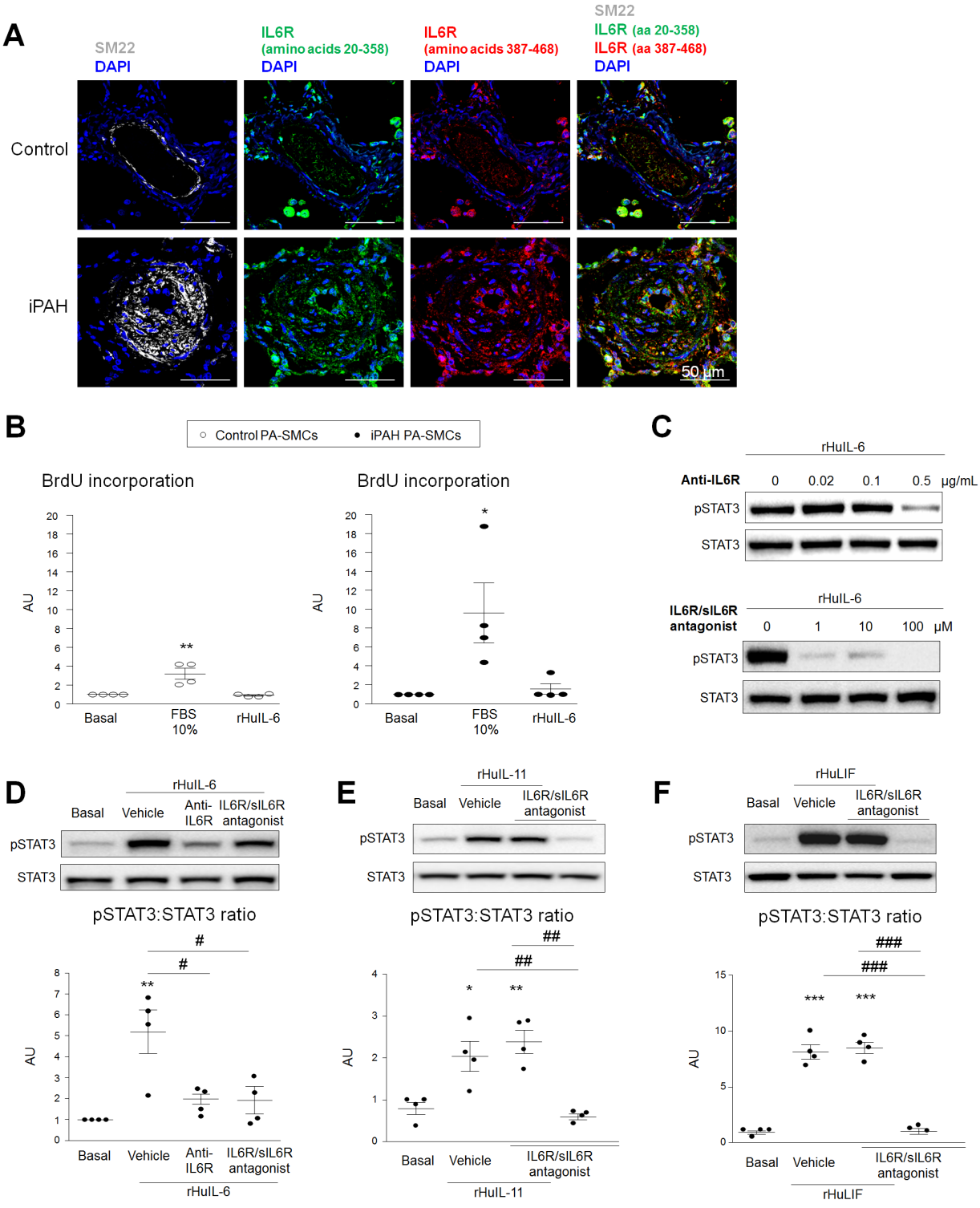
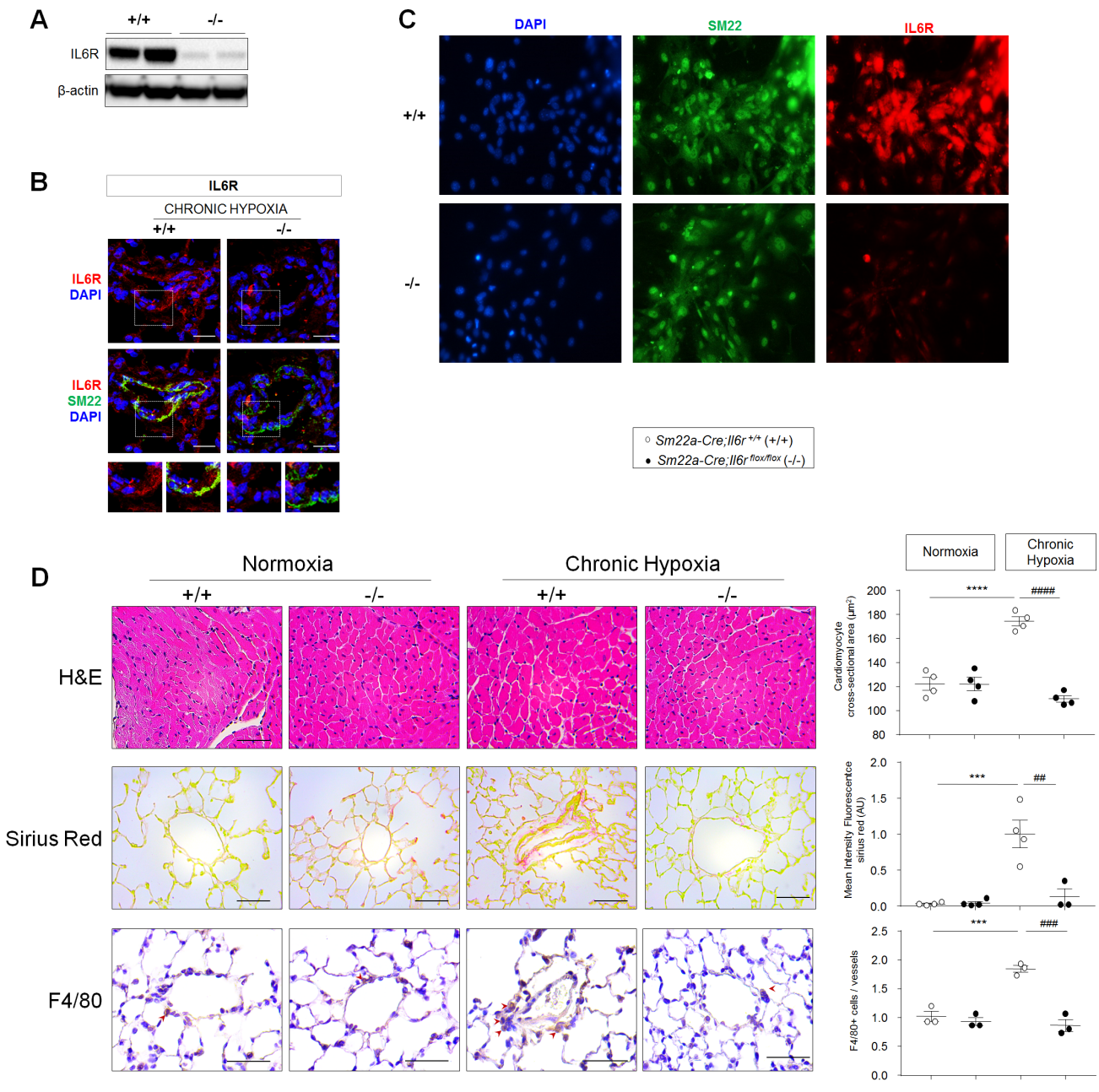
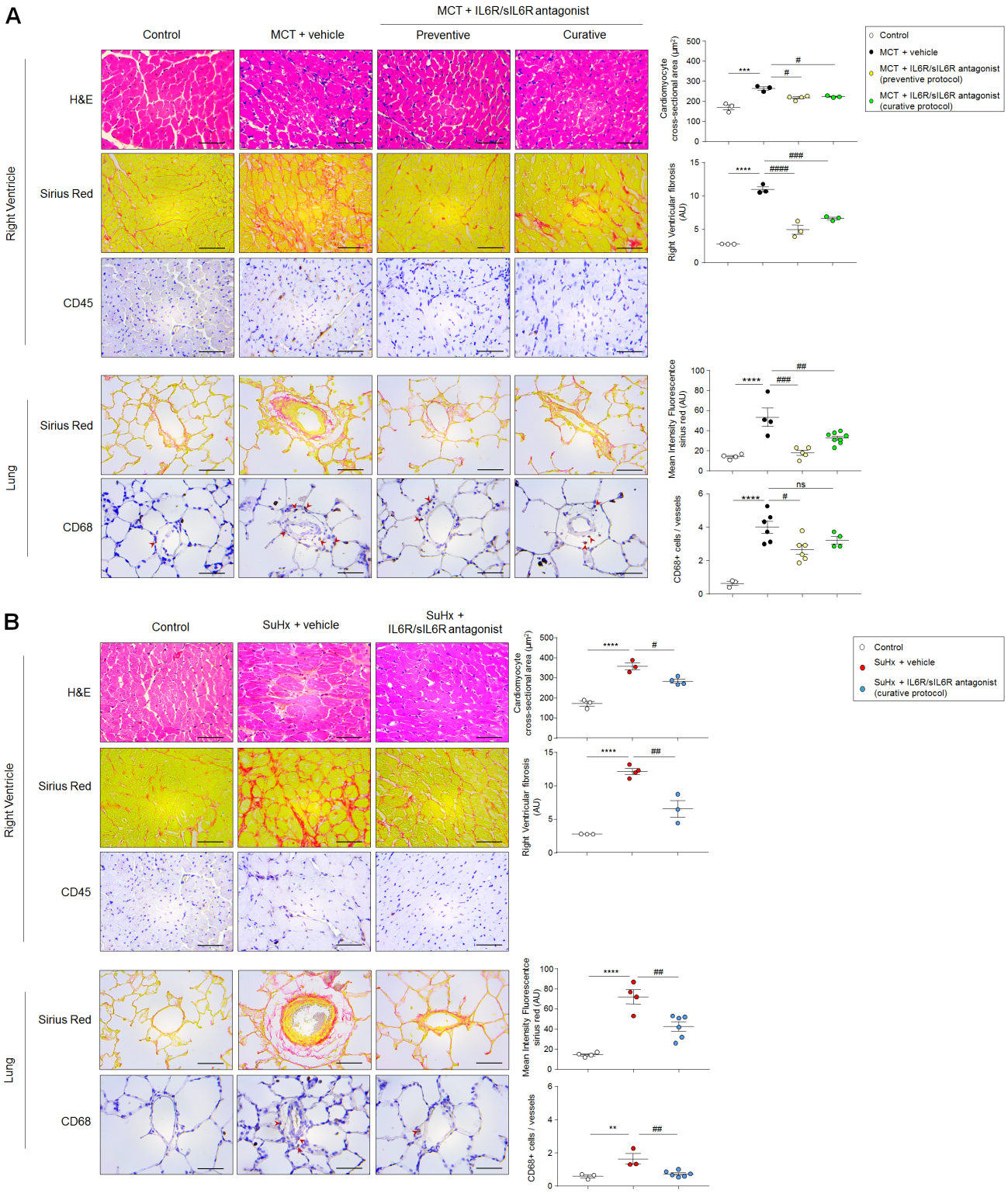


Supplemental Fig. S1 - (A) Double staining with two primary antibodies directed against different antigenic sites of IL6R amino acids 20-358 (green) and 387-468 (red), and SM22 (white) and with DAPI (blue) in lungs from control subjects and patients with idiopathic pulmonary arterial hypertension (iPAH). Of note, the representative images of SM22/DAPI and IL6R (amino acids 20-358)/DAPI in the control lung specimen are from the same experiment as in Figure 1A. **(B)** *In vitro* proliferation analysis of human pulmonary arterial smooth muscle cells (PA-SMCs) isolated from iPAH lung explants and lung specimens from control subjects, under basal conditions or following exposure to 10% fetal bovine serum (FBS) or recombinant human IL-6 (rHuIL-6). PA-SMC proliferation was assessed by 5-bromo-2-deoxyuridine (BrdU) incorporation (n=4). **(C)** Representative Western blots for pSTAT3 and STAT3 in human PA-SMCs derived from iPAH patients after exposure at different doses of a specific neutralizing antibody directed against IL6R (Anti-IL6R) or the nonpeptide IL6R/sIL6R antagonist ERBF (20S, 21-epoxy-resibufogenin-3-formate). Representative Western blots and quantification of the pSTAT3:STAT3 ratio in iPAH PA-SMCs under basal condition or following exposure to either 0.5µg/mL of Anti-IL6R or 10µM of IL6R/sIL6R antagonist in presence of 10ng/mL of recombinant human IL-6 (rHuIL-6) (n=4), **(D)** or 10ng/mL of IL-11 (rHuIL-11) (n=4), **(E)** or 10ng/mL of leukemia inhibitory factor LIF (rHuLIF) (n=3-4). **(F)** *Scale bar=50µm in all sections. Horizontal lines display the mean ± SEM. Comparisons were made using two-way ANOVA with Bonferroni post hoc tests. * p-value < 0.05; ** p-value < 0.01; *** p-value < 0.001 versus basal condition; # p-value < 0.05; ## p-value < 0.01; ### p-value < 0.001 versus iPAH PA-SMCs treated with rHuIL-6 or rHuIL-11 or rHuLIF. AU=arbitrary unit.*



Supplemental Fig. S2 – Supplemental results obtained in transgenic mice deficient in IL6R in the smooth muscle of *Sm22a-Cre;Il6r$^{flox/flox}$ mice*: Representative Western blots for IL6R, β-actin **(A)** and double staining for IL6R and SM22 with DAPI in lungs from *Sm22a-Cre;Il6r$^{flox/flox}$* (-/-) and *Sm22a-Cre;Il6r$^{+/+}$* (+/+) mice under chronic hypoxia **(B). (C)** Double staining for IL6R and SM22 with DAPI in cultured pulmonary artery smooth muscle cells (PA-SMCs) isolated from *Sm22a-Cre;Il6r$^{flox/flox}$* (-/-) mice or *Sm22a-Cre;Il6r$^{+/+}$* (+/+) mice. **(D)** Representative images of hematoxylin-eosin (H&E) and quantification of the cardiomyocytes cross-sectional area in the right ventricle of *Sm22a-Cre;Il6r$^{flox/flox}$* (-/-) mice or *Sm22a-Cre;Il6r$^{+/+}$* (+/+) mice. Representative images of Sirius red staining and F4/80 immunostaining and quantifications in lungs of *Sm22a-Cre;Il6r$^{flox/flox}$* (-/-) mice or *Sm22a-Cre;Il6r$^{+/+}$* (+/+) mice. *Scale bar=50µm in all sections. Horizontal lines display the mean ± SEM (n=3-4). Comparisons were made using two-way ANOVA with Bonferroni post hoc tests. ** p-value < 0.01, *** p-value < 0.001, **** p-value < 0.0001 versus Sm22a-Cre;Il6r$^{+/+}$* (+/+) mice under normoxia. *## p-value < 0.01; ### p-value < 0.001; #### p-value < 0.0001 versus Sm22a-Cre;Il6r$^{+/+}$* (+/+) mice under chronic hypoxia. *AU=arbitrary unit. DAPI=4',6-diamidino-2-phenylindole.*



Supplemental Fig. S3 – Supplemental results obtained in monocrotaline-injected rats and Sugen 5416–treated hypoxic (SuHx) rats treated or not with the IL6R/sIL6R antagonist ERBF (20S, 21-epoxy-resibufogenin-3-formate): (A) *Upper panels:* Representative images of hematoxylin-eosin (H&E), Sirius red staining and CD45 immunostaining with quantifications of the cardiomyocytes cross-sectional area, of collagen deposition in right ventricles of control and monocrotaline (MCT)-injected rats treated or not with the IL6R/sIL6R antagonist ERBF (20S, 21-epoxy-resibufogenin-3-formate) in a preventive or curative approach. *Lower panels:* Representative images of Sirius red staining and CD68 immunostaining with quantifications in lungs of control and monocrotaline (MCT)-injected rats treated or not with ERBF with a preventive or curative approach. **(B)** *Upper panels:* Representative images of hematoxylin-eosin (H&E), Sirius red staining and CD45 immunostaining with quantifications of the cardiomyocytes cross-sectional area, of collagen deposition in right ventricles of control and Sugen 5416–treated hypoxic (SuHx) rats treated or not with ERBF with a curative approach. *Lower panels:* Representative images of Sirius red staining and CD68 immunostaining with quantifications in lungs of control and Sugen 5416–treated hypoxic (SuHx) rats treated or not with ERBF with a curative approach. *Scale bar=50µm in all sections. Horizontal lines display the mean ± SEM (n=3-8). Comparisons were made using two-way ANOVA with Bonferroni post hoc tests. ** p-value < 0.01, *** p-value < 0.001, **** p-value < 0.0001 versus control rats. # p-value < 0.05; ## p-value < 0.01; ### p-value < 0.001; #### p-value < 0.0001 versus vehicle-treated MCT rats or vehicle treated SuHx rats. AU=arbitrary unit.*

Supplemental Table 1

Protein	Source	Clone	Epitope region	Reference	Reactivity	Application
BCL2	Santa Cruz Biotechnology	100	Amino acids 41-54	sc-509	human	Western blot
Bax	Abcam	E63	Amino acids 1-100	ab32503	human	Western blot
CD45	BD Pharmingen	OX-1		550566	rat	Immunostaining
CD68	Santa Cruz Biotechnology	ED1		sc-59103	rat	Immunostaining
F4/80	Santa Cruz Biotechnology	CI:A3-1		sc-59171	mice	Immunostaining
IL-6Rα	Santa Cruz Biotechnology	H300	Amino acids 169-468	sc-13947	mice, rat	Western blot
IL-6Rα	Santa Cruz Biotechnology	D-8	Amino acids 433-460	sc-374259	mice, rat	Immunostaining
IL6-Rα	R&D		Amino acids 20-358	AB-227	human	Western blot, immunostaining
IL6-Rα	R&D	556704	Amino acids 387-468	MAB22771	human	Immunostaining
gp130	Santa Cruz Biotechnology	M-20	Amino acids C-ter	sc-656	human	Western blot, immunostaining
MCL-1	Cell signaling Technology	D35A5		5453S	human	Western blot
p-STAT3	Cell signaling Technology	D3A7		9145S	human, mice, rat	Western blot, immunostaining
STAT3	Cell signaling Technology	124H6		9139S	human, mice, rat	Western blot
β-actin	Sigma-Aldrich	AC-15		A3854	human, mice, rat	Western blot
SM22	Santa Cruz Biotechnology	P15	Internal region	sc-18513	human, mice, rat	Immunostaining
SM22	R&D			AF7886	mice	Immunostaining
α-smooth muscle actin	Novus			NBS300-978	mice	Immunostaining
α-smooth muscle actin	Santa Cruz Biotechnology	1A4		sc-32251	mice, rat	Immunostaining