Supplementary material

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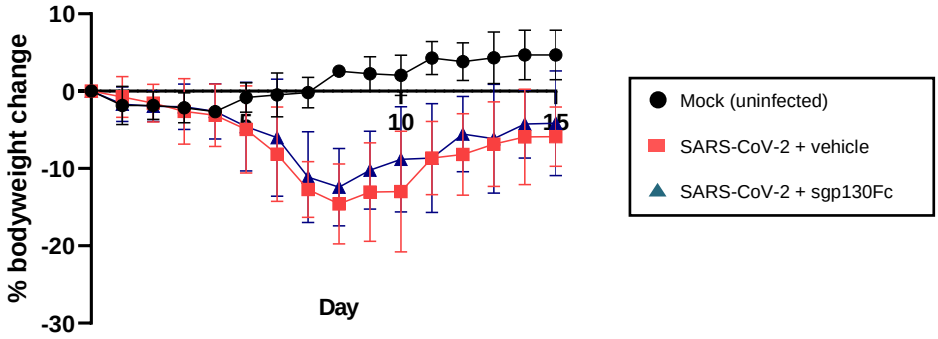
Table S1. qPCR primers for detection of mouse (m) and human (h) genes.

Gene	Sequence (5' – 3')	Gene	Sequence (5' – 3')
mCyclophilin	Fw: GTCTCCTTCGAGCTGTTTGC	mhRplo	Fw: AACATCTCCCCCTTCTCCTT
	Rv: CGTGTAAAGTCACCACCCTG		Rv: GAAGGCCTTGACCTTTTCAG
mIl6r	Fw: ACGAAGGCTGTGCTTTGC	mIl6st	Fw: AAGGATTTGGCTAGCGCAAGC
	Rv: TTCGTTGTGGCTGGACTTGC		Rv: CCACACGATGTAGCTGGCATT
mOsm	Fw: ACGGCTTCTAAGAACACTGC	mOsmr	Fw: TCTTGGAGGAGCCTTTACCAT
	Rv: GATATAGGGCTCCAAGAGTG		Rv: TTTCCAGGAACTCCAGTTGC
mLif	Fw: CGAGACCACGCTCCAGTATAT	mLifr	Fw: CGATGCATGCAAACGGTCTGA
	Rv: TTTCCAGTGCAGAACCAGCAG		Rv: GACTTCGTGATCACCAGGTGA
mIl11	Fw: ACTAGCTGCACAGATGAGAG	mIl11r	Fw: CCTGGAGACATCTGTCCTCA
	Rv: GCTCCAGAGTCTTTAGGGAA		Rv: CCTGAGCAGCTGCTGCTCAT
mSocs3	Fw: AAGGCCGGAGATTTCGCT	mSaa1	Fw: TTGTTCACGAGGCTTTCC
	Rv: AACTTGCTGTGGGTGACCAT		Rv: TGAGCAGCATCATAGTTCC
mLrg1	Fw: TAGAGGAGCAGCTATGGTCTCT	mTnfα	Fw: AGCCCACGTCGTAGCAAACC
	Rv: TACCCTCAGCCGACTGCAGTAT		Rv: GAGGAGCACGTAGTCGGGGC
mIl1β	Fw: CTTGGGATCCACACTCTCCAG	mIfnγ	Fw: ACAGCAAGGCGAAAAAGGA
	Rv: AAATACCTGTGGCCTTGGGC		Rv: TGGTGGACCACTCGGATGA
mIL10	Fw: GCTCTTACTGACTGGCATG	mRORgt	Fw: AAGGCAAATACGGTGGTGTG
	Rv: CCTGAGGGTCTTCAGCTTC		Rv: GAAAAGGGTGAAGGAGTCGC
mSTAT3	Fw: GGAGCAGCATCTTCAGGATGT	mFOXP3	Fw: GAGAAGACAGACCCATGCTGT
	Rv: TCTGTCTGGTCACAGACTGGT		Rv: AGAGGAGCTGCTGAGATGTGA
mIL17	Fw: TCCAGGGAGAGCTTCATCTG		
	Rv: GAAGTCCTTGGCCTCAGTGT		
hCyclophilin	Fw: AGACAAGGTCCCAAAGACAGC	hIl6	Fw: TGACCCAACCACAAATGC
	Rv: CAGTGCCATTATGGCGTGTGA		Rv: CTGGCTCTGAAACAAAGGAT
hgp130	Fw: TTGACGTTGCAGACTTGGCT	hCcl2	Fw: GCAAGTGTCCCAAAGAAGCT
	Rv: AACTGGAGATTCAGGACTGA		Rv: AGCTTCTTTGGGACACTTGC
hCxcl2	Fw: GCAGAAAGCTTGTCTCAACCC	hIcam	Fw: AGGATGGCACTTTCCCACTG
	Rv: GGCAGAAAGCTTGTCTCAACCC		Rv: GGAGAGCACATTCACGGTCA

Table S2. Clinical sickness parameters

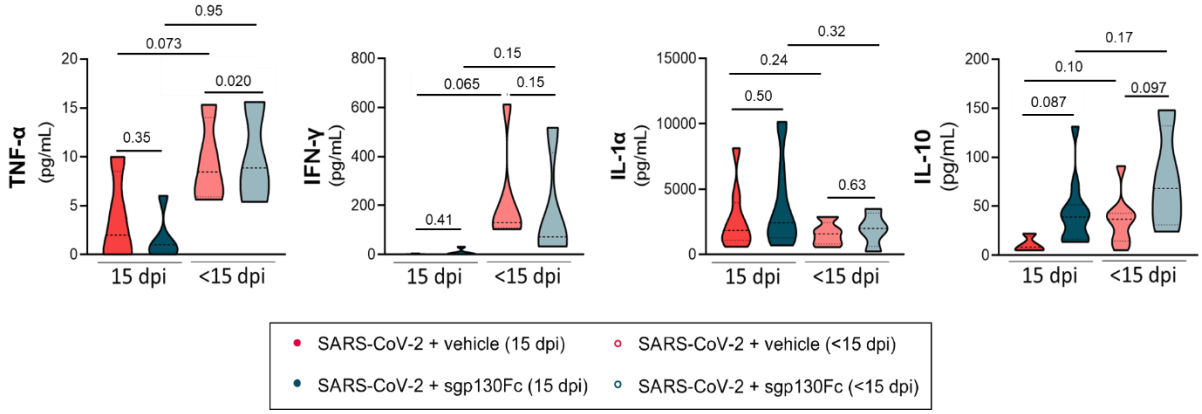
Clinical parameters		Degree
Breathing	Dyspnoea	No Yes
Appearance	Piloerection	No Yes
	Hunched posture	No Yes
	Eye closure	Normal Squinted/Closed
Behavior	Spontaneous	Alert Slow moving/Lethargy
	Provoked	Response to stimuli No response to stimuli

Fig. S1



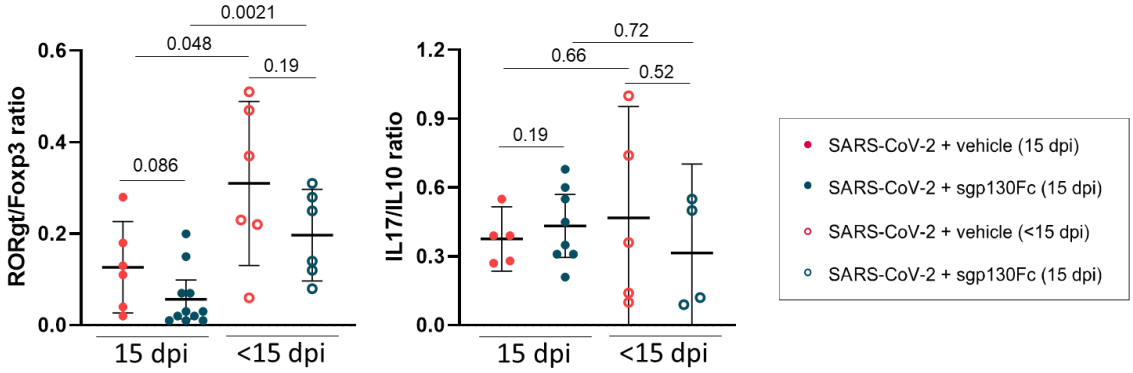
Percentage of body weight change in SARS-CoV-2 K18-hACE2 infected mice. Data are shown as mean and 95% confidence intervals (CI). Data are combined from two independent experiments.

Fig. S2



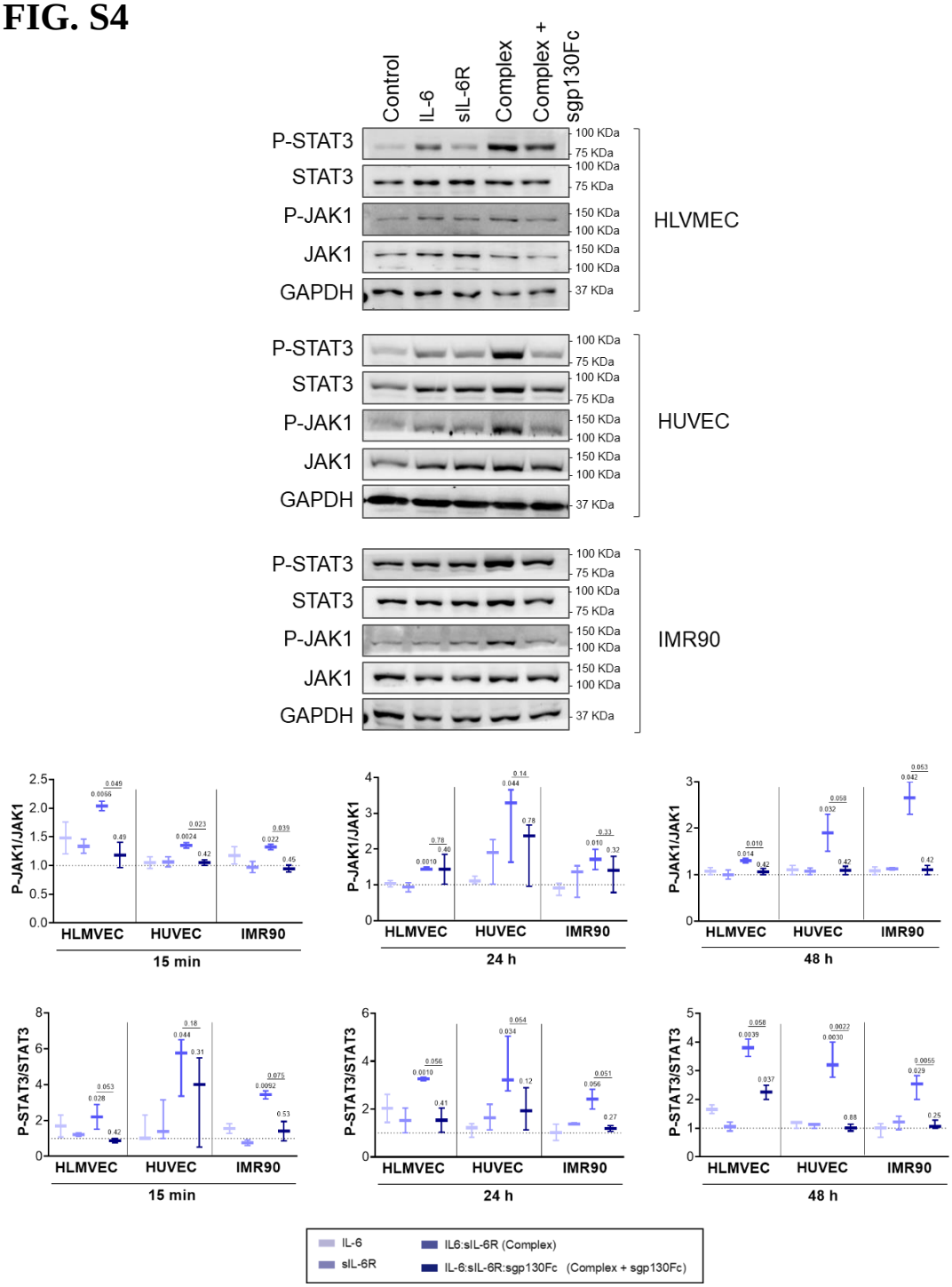
Serum cytokines and chemokines levels from SARS-CoV-2-infected mice. Serum from untreated and sgp130Fc-treated infected animals were analysed by multiplex analysis. Data are combined from two independent experiments. dpi: day post infection. < 15 dpi: dead/euthanized mice before the end of the experiment. 15 dpi: surviving mice at the end of experiment. All graphs show mean and 95% CI. Statistics were calculated by Kruskal-Wallis test with Mann-Whitney U-test. p values are indicated in the graphs.

Fig. S3



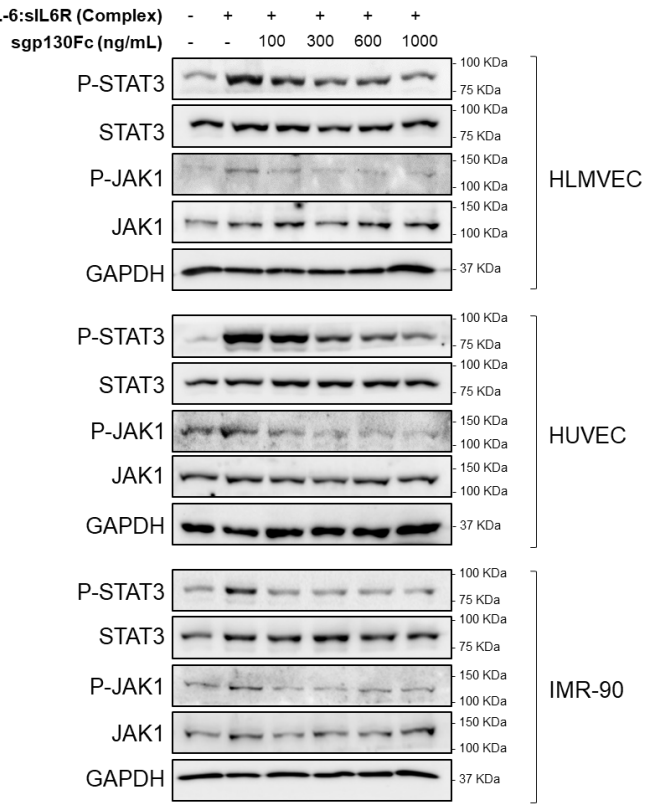
Treg related factors (*Foxp3* and *Il-10*) and Th17 related factors (*Rorγt* and *Il17*) in infected mice. Rorγt/Foxp3 and IL17/IL-10 mRNA ratios measured in lung homogenates by qPCR**.** Data are combined from two independent experiments. dpi: day post infection. < 15 dpi: dead/euthanized mice before the end of the experiment. 15 dpi: surviving mice at the end of experiment. All graphs show mean and 95% CI. Statistics were calculated by Kruskal-Wallis test with Mann-Whitney U-test. *p* values are indicated in the graphs.

FIG. S4



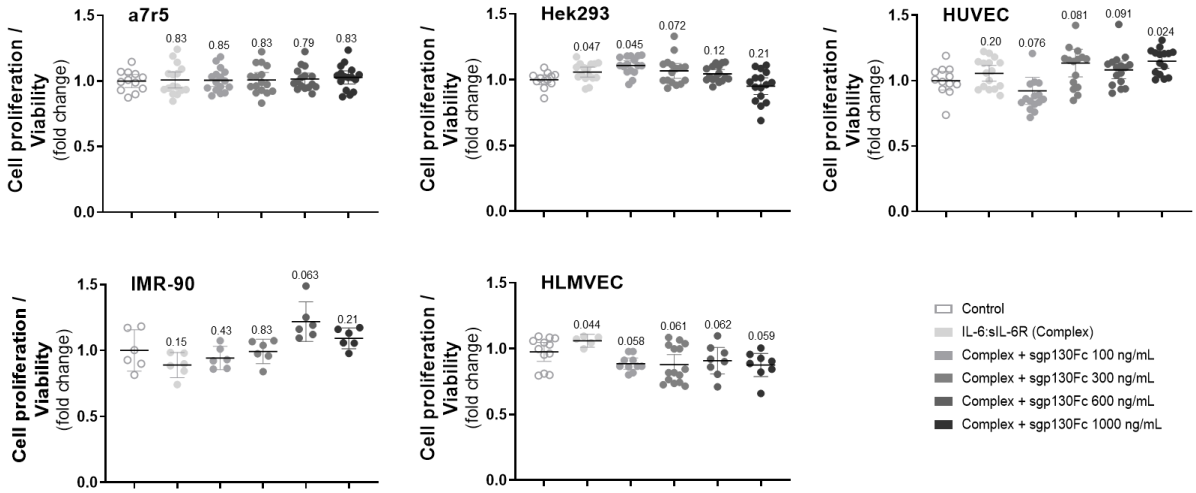
JAK1/STAT3 signalling on human primary endothelial cells and fibroblasts. a) Representative Western blots P(Tyr705)-STAT3, STAT3, P(Tr1034/1035)-JAK1 and JAK1 from cell lysates after 48 h of treatment. b) Western blot densitometric analyses of P(Tyr705)-STAT3/STAT3 and P(Tyr1034/1035)-JAK1/JAK1 at 15 min, 24 h (presented in Fig 7a) and 48 h. Human lung microvascular cells (HLMVEC), human umbilical vein endothelial cells (HUVEC) and primary lung fibroblast (IMR-90) were treated with vehicle, IL-6 (20 ng/mL), IL-6R (20 ng/mL) or IL-6:sIL-6R complex (20 ng/mL) in the presence or absence of sgp130Fc (300 ng/mL). Data are combined from 4-3 individual experiments. Control is set to 1 for each experiment and data presented as fold-change *vs* control. Complex: IL-6:sIL-6R complex. Complex + sgp130: IL-6:sIL-6R:sgp130Fc complex. All graphs show mean and 95 % CI. Statistics were calculated by Kruskal-Wallis test with Mann-Whitney U-test. *p* values *vs* vehicle-treated control (above) and *vs* complex (bar) are indicated in the graphs.

Fig. S5



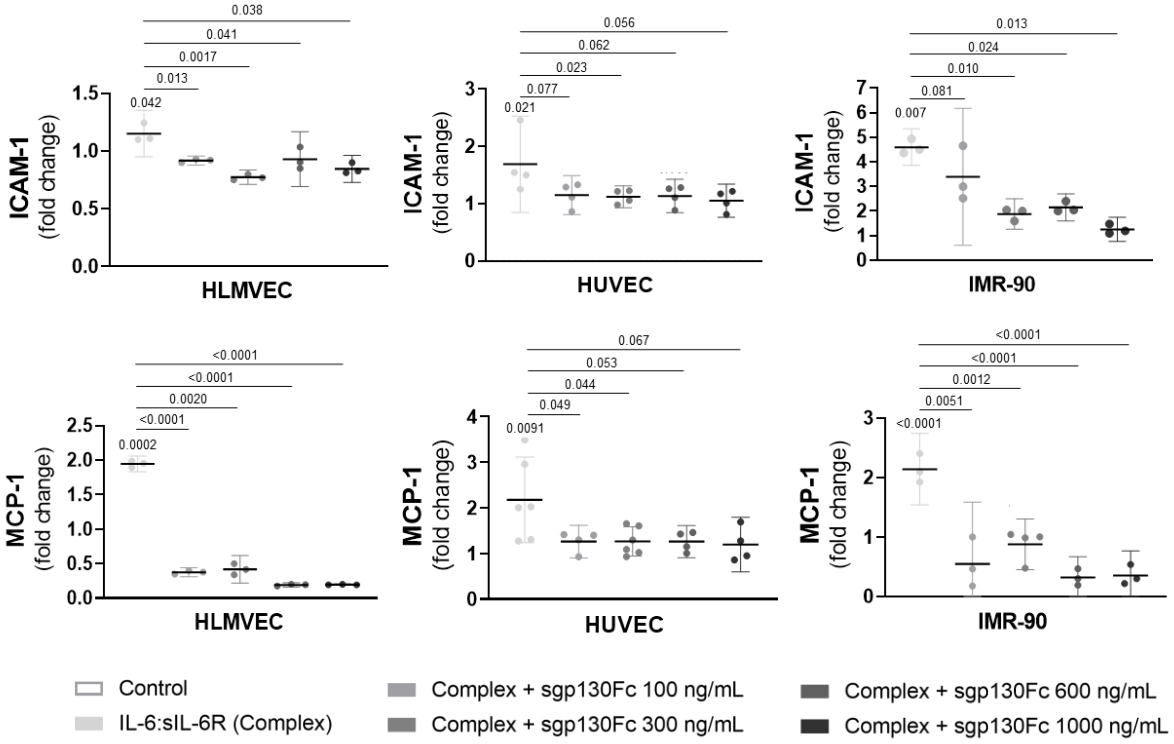
sgp130Fc blocks IL-6:sIL-6R complex stimulation in a dose dependent manner. Representative Western blots of P(Tyr705)-STAT3, STAT3, P(Tr1034/1035)-JAK1 and JAK1 in Human lung microvascular endothelial cells (HLMVEC), human umbilical vein endothelial cells (HUVEC) and human lung fibroblast (IMR-90) treated during 24 h with IL-6:sIL-6R complex in the presence or absence of different doses of sgp130Fc (100 ng/mL, 300 ng/mL, 600 ng/mL, 1000 ng/mL).

Fig. S6



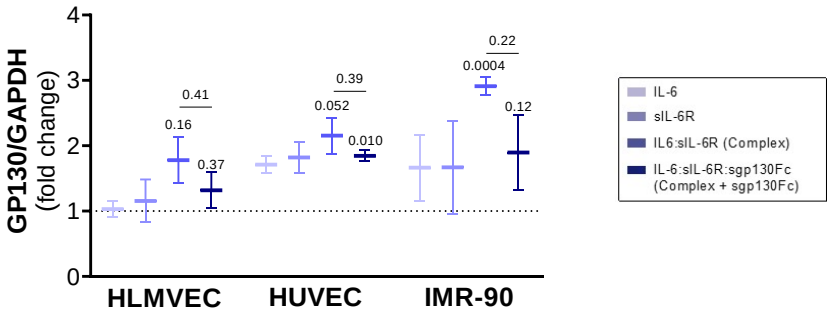
Cell proliferation/viability after sgp130Fc treatment. Human lung microvascular endothelial cells (HLMVEC), human umbilical vein endothelial cells (HUVEC), human lung fibroblast (IMR-90), aortic thoracic smooth muscle cells (A7r5) and human embryonic kidney cells (HEK293) were seeded in 96-well plates at a density of 5000 or 10,000 cells/well (for cell lines or primary cell culture, respectively) and serum starved for 24 h. Then, cells were treated with vehicle (control) and IL-6:sIL-6R (Complex, 20 ng/mL) in the presence or absence of different doses of sgp130Fc (100 ng/mL, 300 ng/mL, 600 ng/mL, 1000ng/mL) for 24 h. Proliferation/viability was evaluated using AlamarBlue reagent (Biosource International) and determined in a Spectrophotometer (Thermo Scientific Multiskan Go Microplate) up to 72 h. Results were expressed as a percentage referred to vehicle-treated controls. Data are combined from 6-16 independent experiments. Control is set to 1 for each experiment and data presented as fold-change *vs* control. All graphs show mean and 95% CI. Statistics were calculated by one way ANOVA.

Fig S7



ICAM-1 and MCP-1 secretion from cultured human endothelial cells and lung fibroblasts. Human lung microvascular endothelial cells (HLMVEC), human umbilical vein endothelial cells (HUVEC) and human lung fibroblast (IMR-90) were treated with vehicle (control), IL-6 (20 ng/mL), IL-6R (20 ng/mL) or IL-6:sIL-6R (Complex, 20 ng/mL) in the presence or absence of sgp130Fc (100 ng/mL, 300 ng/mL, 600 ng/mL, 1000 ng/mL). ICAM-1/CD54 and CCL2/MCP1 levels by ELISA after 12 h and 24 h of treatment respectively. Data are combined from 3-4 independent experiments. Control is set to 1 for each experiment. All graphs show mean and 95% CI. Statistics were calculated by Kruskal Wallis test and with Mann-Whitney U-test. *p* values are indicated in the graphs.

Fig. S8



Western blot densitometric analyses of gp130. Human lung microvascular cells (HLMVEC), human umbilical vein endothelial cells (HUVEC) and primary lung fibroblast (IMR-90) were treated with vehicle, IL-6 (20 ng/mL), IL-6R (20 ng/mL) or IL-6:sIL-6R complex (20 ng/mL) in the presence or absence of sgp130Fc (300 ng/mL) for 24 h. Data are combined from 3 individual experiments. Control is set to 1 for each experiment and data presented as fold-change vs control (mean and 95% CI). Complex: IL-6:sIL-6R. Complex + sgp130: IL-6:sIL-6R:sgp130Fc. Graph shows mean and 95% CI. Statistics were calculated by Kruskal-Wallis test with Mann-Whitney U-test. *p* values *vs* vehicle-treated control (above) and versus complex (bar) are indicated in the graphs.