

Mice	Reduction of mRNA
Hif1 $\alpha^{fl/fl}$;UbcCreERT ⁺	Hif1 α : -80% \pm 5%
Hif2 $\alpha^{fl/fl}$;UbcCreERT ⁺	Hif2 α : -71% \pm 6%
Hif2 $\alpha^{fl/WT}$;UbcCreERT ⁺	Hif2 α : -36% \pm 4%
Hif1 α -ASO	Hif1 α : -60% \pm 5% (RV)
Hif2 α -ASO	Hif2 α : -72% \pm 4%

Supplementary Table 1. Hif1a and HIF2a mRNA reduction in floxed and ASO treated mice. Rate of reduction in Hifa mRNA after hypoxia exposure (experimental setup: Fig. 1A and Fig. 3C)) in cre-positive mice and in ASO-treated animals, compared to the appropriate controls (cre-negative mice or Ctrl-ASO). Similar results were obtained for normoxic animals (data not shown). Expression was studied in lung tissue, with the exception of Hif1 α ASO, for which RV tissue was used (no lung tissue available). There was no reduction of Hif1 α , when Hif2 α was targeted and vice versa.

	Sea Level		18,000ft	
	Hif1 $\alpha^{fl/fl}$; <i>UbcCre-</i>	Hif1 $\alpha^{fl/fl}$; <i>UbcCre+</i>	Hif1 $\alpha^{fl/fl}$; <i>UbcCre-</i>	Hif1 $\alpha^{fl/fl}$; <i>UbcCre+</i>
Weight (g)	29.3	27.3	24.2 (**)	22.0 (**)(^)
Females / Males (n)	6/3	9/2	3/7	5/4
Heart Rate (bpm)	366	340	448 (***)	435 (*)

Supplementary Table 2. Parameters were taken after exposure to either sea level or high altitude at the end of the experiment. *, ** and ***: p<0.05, p<0.01 and p<0.001 for sea level vs. high altitude within the same genotype. ^p<0.1 for cre-negative vs. Cre-positive within the same condition. T-test was used.

	Sea Level		18,000ft	
	Hif2 $\alpha^{fl/WT};$ <i>UbcCre-</i>	Hif2 $\alpha^{fl/WT};$ <i>UbcCre+</i>	Hif2 $\alpha^{fl/WT};$ <i>UbcCre-</i>	Hif2 $\alpha^{fl/WT};$ <i>UbcCre+</i>
Weight (g)	25,0	26,3	23,5	23,1
Females / Males (n)	5/2	1/3	3/7	5/7
Heart Rate (bpm)	397,1	390,0	390,0	360,0

Supplementary Table 3. Parameters were taken after exposure to either sea level or high altitude at the end of the experiment.

	Sea Level		18,000ft	
	<i>Ctrl-ASO</i>	<i>Hif2a-ASO</i>	<i>Ctrl-ASO</i>	<i>Hif2a-ASO</i>
Weight (g)	27,6	26,2	23,3 (**)	22,4 (***)(^)
Females / Males (n)	0/8	0/8	0/8	0/7
Heart Rate (bpm)	386,7	340,5	500,5 (**)	406,4 (##)

Supplementary Table 4. Parameters were taken after exposure to either sea level or high altitude at the end of the experiment. **, ***: $p < 0.01$ and $p < 0.001$ for sea level vs. high altitude within the same ASO-treatment group. ^, ##: $p < 0.1$ and $p < 0.01$ for Ctrl-ASO vs. Hif2a-ASO within the same condition. T-test was used.

	Sea Level		18,000ft	
	Hif2 $\alpha^{fl/fl}$, <i>EC-Cre-</i>	Hif2 $\alpha^{fl/fl}$, <i>EC-Cre+</i>	Hif2 $\alpha^{fl/fl}$, <i>EC-Cre-</i>	Hif2 $\alpha^{fl/fl}$, <i>EC-Cre+</i>
Weight (g)	23,8	25,7	22,4	21,3
Females / Males (n)	5/4	4/4	4/3	6/1

Supplementary Table 5. Parameters were taken after exposure to either sea level or high altitude at the end of the experiment.

Gene		Mouse	Rat	Human
Acta1	fwd	AATGCTTCTAGGCGACTCG		
	rev	CCTGCAACCACAGCACGATT		
Adm	fwd	GACAAAGACAAGGACGGCATG	GGTATCGGAGCATCGCTACAG	GAG TGG AAG TGC TCC CCA CTT
	rev	GCCTTGAGGGCTGATCTTGTT	GAACGGCGAGCGAACCCAAT	CTT GTA CCA TGG GCG CCT A
Apln	fwd	GACCGAGTTGCAGCATGAATC	TGCCACTGATGCTGCCTCCA	ATGAATCTGCGGCTCTGCGT
	rev	TCAAGGAGAGCCAGAGCAGC	CTTCACCAGGTAGCGCATGTT	GCGGCATCAGGGACCCTCC
Arg1	fwd	GCTTGCGAGACGTAGACCCT	CAGAGGAGGTGACTCGTACTGTG	ACTCGAACAGTGAACACAGCAGT
	rev	TGCCAATCCCAGCTTGTCT	ACAAGACAAGGTCAACGCCA	CAATAGGCTTGTGATTACCCTCC
Arg2	fwd	GAAGAGGCCAAGGCAACAGC	AGGCTGCACTCACTCGAGGT	AATCCTCAGTTGGCCACCTC
	rev	TGTCCTCCTTCTTGTCTGACC	ATGATTGGCAGGGAGGCGAT	CAATCACATCTACTGCCAGGTTAGC
Bcl2				TCCACCAAGAAAGCAGGAAAC
				TGGACAGGATAGCAGCACAGGA
Bcl2L1				CAG GAG AAC GGC GGC TGG GA
				TCG GCT GCT GCA TTG TTC CCA
Birc5				GTGGCTGCTTCTCTCTCTCT
				GCCTTCTCCTCCCTCACTT

Supplementary Table 6. Primer sequences used for qRT-PCRs.

Gene		Mouse	Rat	Human
Bmpr2	fwd	AGAAGAGCACAGAGGCCCAAT	GTC TAC ACA GTG TGA GCA TGA TGG	TGCTATGCAGAATGAACGCAAC
	rev	CTGTATACTGCTGCCATCCAGG	CTC CAG CAG CTT CAG GTT ATC CAA	AAGGACCAATTTTGGCACACG
Ca9	fwd	TGAAGGGTCTCTGACCACACC	CTGCCTCTCTGCTGGTGACA	GGT GTC ATC TGG ACT GTG TTT
	rev	ACACAGTCCAGATGACCCCC	AGGAGGAAGGCGATGCTGGT	GGT GTC AGA GAG GGT GTG GAG
Ccl2	fwd			CATGAAAGTCTCTGCCGCCT
	rev			TGAGCGAGCCCTTGGGGAAT
Ccna1	fwd		CTTCAGTACTTAAGGCGGCAA	
	rev		GGCCAAATTCTCAGTCCTGATG	
Ccnd1	fwd	CGT GGC CTC TAA GATGAA GGA	ATGGTGGCTGCTGGGAGTGT	CGT GGC CTC TAA GATGAA GGA
	rev	GTA GAT GCA CAG CTT CTC GGC	TAGCAGGAGAGGAAGTTGTTGG	GTA GAT GCA CAG CTT CTC GGC
Ccne1	fwd			GGACACCATGAAGGAGGACG
	rev			TTCCTGGAGCGAGCCGAGAA
Ccne2	fwd			GTAGCTGGTCTGGCGAGGTT
	rev			ACGGCTACTTCGTCTTGACATTC
Cd68	fwd	CACAGGCAGCACAGTGGACA	CTTTGGATTCAAACAGGACCG	
	rev	CTTGGAGCTCTCGAAGAGATGA	GGTAGACTGTACTGTGGCTCTGATG	

Supplementary Table 6 (continued). Primer sequences used for RT-PCRs.

Gene		Mouse	Rat	Human
Cxcr4	fwd	CCCTCGCCTTCTTCCACTG	TGTTCCAGTTCAGCACATC	ATCTGTGACCGCTTCTACCCC
	rev	CGAGGAAGGCATAGAGGATGG	CCTTGGAGTGTGACAGCTTG	AAACTGGAACACAACCACCCA
Edn1	fwd	GCACCGGAGCTGAGAATGGA	CGAGCTGAGAAGGAAGTCAGAG	AAAGAGTGTGTCTACTTCTGCCACC
	rev	ACAGGAACAGCGCTTGGACC	AAGGAGGAGCAGGAGCAACG	CAACGTGCTCGGGAGTGTTG
Epo	fwd	TTGGAAAAGAATGGAGGTGGA		
	rev	GACAGGCCTTGCCAACTTC		
Glut1	fwd	GGA GAG GTG TCA CCT ACA GC	GATGATGCGGGAGAAGAAGG	TGTGGGCCTTTTCGTTAACC
	rev	AAG GAT GCC AAC GAC GAT TC	AGCACCACGGCGATGAGGAT	ATCATCAGCATTGAATCCGC
Hif1a	fwd	TGCAGCAAGATCTCGGCGAA		TTT TAC CAT GCC CCA GAT TCA
	rev	AGTGGCAACTGATGAGCAAGC		AGT GCT TCC ATC GGA AGG ACT
Hif2a (Epas1)	fwd	GACGGAGGTCTTCTATGAGTTGG		TACAAGGAGCCCTGCTGTC
	rev	CGCATGATGGAGGCTTTGTC		TGCTGGATTGGTTCACACATG
Icam1	fwd	GAGGAGATACTGAGCCGCCA	CTTCCGACTAGGGTCCTGAA	CTGTATACTGCTGCCATCCAGG
	rev	GCTAGCCAGCACCGTGAATG	CTTCAGAGGCAGGAAACAGG	CTGGCTTCGTCAGAATCACGTT
Id1	fwd	GGTGGAGATCCTGCAGCATGTA	TTC TGC TCT ACG ACA TGA ACG GCT	GCACCCTCAACGGCGAGATCAGCG
	rev	CCGACTTCAGACTCCGAGTTCA	ACA TGC TGC AGT ATC TCC ACC TTG	CAGCGACACAAGATGCGATCGTCC

Supplementary Table 6 (continued). Primer sequences used for qRT-PCRs.

Gene		Mouse	Rat	Human
Id3	fwd	GGAACGTAGCCTGGCCATT	CTG TCG GAA CGT AGC CTA GCC ATT	CAG CGC GTC ATC GAC TAC ATT CTC
	rev	TCCAAGAGGCTAAGAGGCTCC	GCG AGT AGC AGT GGT TCA TGT CGT	CCA TCA GGG GGT CCA GGG GCT GGC
Myh6	fwd	GGGCAGCTCATGCGCATTGA		
	rev	TGCGCTCTTCAGCAGCGGTT		
Myh7	fwd	CAGCAGTTGGATGAGCGACT		
	rev	GATGCGTGCCTGAAGCTCCT		
Ndrgr1	fwd	ATGCCTGGAACCCACACTGT	GTGGAGGTGGTGACACGTA	GAA GCA AGC ATC TCC GCA TC
	rev	AACTACCAGCCAGAGCAGGGC	TTGTAGGCGCTGATGAACAGG	CAA CCG GCC ACT GGT TAA TG
Pai1	fwd	TTTGGACCCAGTTCCCACC	TTGTGAAGGAGGAACGCTGC	
	rev	TGAAAGTGTTGTGCCCTCCAC	ATTGGCTCTTGTGGCTGTCG	
Pdgfrb	fwd	AATGCTGAGCGACCACTCCA	CAGCAGAGCCTGCCGTAATC	GGCCGAGTTGGACCTGAACA
	rev	TACGGAGTCTCTGTGCAGCAGG	GAACACCTCTGTACGCGTCTTG	TCCAGCTCGCTCCAGAGTG
Pgk1	fwd	GGAGAGTCCAGAGCGACCCCT		
	rev	GCAACTTTAGCGCCTCCCA		
Sdf1	fwd	ATCGGTGGCTGCGAGCTGAA	TGTGCATTGACCCGAAATTA	AGA TTG TAG CCC GGC TGA AG
	rev	ACATGCCTGGGATGCTGCGT	TCCTCAGGGGTCTACTGGAA	TCG GGT CAA TGC ACA CTT GT

Supplementary Table 6 (continued). Primer sequences used for qRT-PCRs.

Gene		Mouse	Rat	Human
Tgfa	fwd	GGGAAGGAAATGTGTTCCCTG	CAACAAGTGCCCAGATTCCC	GAAGGGAAGAACCGCTTGCT
	rev	GGCTCAATGGGTCAGAGCAT	GGCTTCTCTTCTGCACCAA	TGGGCTCTTCAGACCACTGTT
Tnc	fwd		TGCTGAAGGTTGTGGCTGTG	
	rev		ATTCAGGCTCAGAGCAGTTGG	
Tsp1	fwd	CAATTTTCAGGGGGTGCTGC	ACATCTGCTCTGTACCTGTGG	CCTGTGATGATGACGATGA
	rev	CCGTTCCACCAGTTGTTGTC	GGGTTGTTGCAGAGTCGGCT	CTGATCTGGGTTGTGGTTGTA
Vegf	fwd	TGACAAGCCAAGCGCGTGAG	GGGATCTTTCATCGGACCAGT	TGT GCC CAC TGA GGA GTC C
	rev	CTCCTCTTCCTTCATGTCAG	CGGTGTCTGTCTGTCTGTCCGT	GGT TTG ATC CGC ATA ATC TGC
House keeping:				
18S	fwd	GAA TTC CCA GTA AGT GCG GG (for mouse, rat and human)		
	rev	GGG CAG GGA CTT AAT CAA CG (for mouse, rat and human)		
Actb	fwd	GCCCTGAGGCTCTTTCCAG	CCAGCCATGTACGTAGCCATCCAG	GCCCTGAGGCACTCTTCCA
	rev	TGCCACAGGATTCCATACCC	TCACAATGCCAGTGGTACGACCAG	ATGCCACAGGACTCCATGC

Supplementary Table 6. Forward and Reverse sequences of qPCR primers used in the manuscript, listed in mouse, rat, and human genes. The amplicon sizes are typically 50-80 mer and without significant secondary structures. All primer sets were validated by melt curve analysis, cloning and sequencing of qPCR products, and standard dilution assay to ensure specific PCR products and to have amplification efficiencies between 90% and 110%. *Hif1α* floxed mice and *Hif-2α* floxed mice were constructed wherein exon 2 (coding DNA binding domain) of the *Hif1α* or *Hif2α* gene was floxed with LoxP sites. To assess HIF1a and HIF2a deletion in HIF flox mice, qPCR primers for mouse HIF1a and HIF2a mRNAs are located in the exon 2 of HIF1α or HIF2α gene.

	Gene	Cell type	Normoxia	Hypoxia
Hypoxic induction of classical HIF target genes In normal pulmonary artery vascular cells	ADM	EC	100%±9.7	250.7%±24.3***
		Fib	100%±0.6	221.3%±41.2***
		SMC	100%±22.3	93.7%±6.8
	CA9	EC	100%±10.1	1328.6%±274.4*
		Fib	100%±18.6	19164.2%±3575.7**
		SMC	100%±26.7	235.1%±26.7
	GLUT1	EC	100%±27	301.3%±33***
		Fib	100%±1.6	477.0%±8.7***
		SMC	100%±20.2	461.7±140.2***
	NDRG1	EC	100%±8.6	301.8%±15.6***
		Fib	100%±8.7	333.5%±30.3***
		SMC	100%±9.6	312.6%±13.6***
	VEGF	EC	100%±8.2	193.5%±6.9***
		Fib	100%±5.3	208.5%±27.1***
		SMC	100%±7.2	209.6%±30***
Hypoxic induction Of inflammatory genes in normal pulmonary artery vascular cells	CXCR4	EC	100%±4.8	250.0%±13.2***
		Fib	100%±2.9	46.3%±23.9
		SMC	100%±3.3	195.6%±18.2***
	SDF1	EC	100%±13.9	321.5%±13.9***
		Fib	100%±0.61	123.2%±53.0
		SMC	100%±3.3	109.4%±32.42
	ICAM1	EC	100%±23.6	307.4%±18.8***
		Fib	100%±3.7	138.6%±4.4
		SMC	100%±41.6	162.7%±18.8

Supplementary Table 7. Gene expression in pulmonary artery cells by qRT-PCR, as in Fig. 6. Statistical significance as determined by t-test.

	Gene	Cell type	Normoxia	Hypoxia
Hypoxic induction Of signaling factors in normal pulmonary artery vascular cells	APLN	EC	100%±12.0	208.3%±57.7***
		Fib	100%±52.7	595.8%±64.5***
		SMC	100%±4.3	530.%±16.4***
	ARG1	EC	100%±30.8	89.4%±15.4
		Fib	100%±21.3	89.8%±32.3
		SMC	100%±39.8	82.7%±4.9
	ARG2	EC	100%±22.4	97.9%±11.2
		Fib	100%±15.5	79.0%±10.1
		SMC	100%±8.7	87.2%±27.3
	BMPR2	EC	100%±16.5	94.7%±17.1
		Fib	100%±25.1	127.8%±15.4
		SMC	100%±27.0	76.6%±15.0
	CCND1	EC	100%±5.1	103%±6.1
		Fib	100%±9.6	90%±5.8
		SMC	100%±30.8	110%±32.7
	EDN1	EC	100%±13.1	118.0%±22.7
		Fib	100%±38.3	366.5%±17.4***
		SMC	100%±25.0	144.7%±8.9***
	ID1	EC	100%±14.7	30.0%±4.3***
		Fib	100%±12.3	83.6%±12.3
		SMC	100%±14.4	96%±7.1
	ID3	EC	100%±4.6	54.8%±12.0***
		Fib	100%±4.3	96.4%±6.0
		SMC	100%±10.0	91.2%±1.2

Supplementary Table 7, continued.

	Gene	Cell type	Normoxia	Hypoxia
Hypoxic induction Of signaling factors in normal pulmonary artery vascular cells (continued)	PDGFB	EC	100%±25.7	161.2%±23.3*
		Fib	100%±33.5	120.1%±12.0
		SMC	100%±43.2	257.3%±39.6**
	TGFA	EC	100%±17.8	775.3%±127.1***
		Fib	100%±23.0	80%±15.0
		SMC	100%±60.0	346.9%±16.9***
	TSP1	EC	100%±20.1	104.0%±4.6
		Fib	100%±8.1	141.7%±28.1
		SMC	100%±30.0	159.9%±62.5*

Supplementary Table 7, continued.

	Gene		Normoxia	Hypoxia	Δ
Hypoxic induction of classical HIF target genes in EC	GLUT1	DMSO	100.0%±1.2	721.26%±75.1***	
		PT2567 0.1μM	103.0%±13.3	555.5%±20.8***	23% [#]
		PT2567 1μM	88.9%±14.62	346.8%±21.2**	36.5% ^{###}
		PT2567 10μM	116.7%±19.6	242.6%±84.4*	51.9% ^{###}
	NDRG1	DMSO	100.0%±12.6	603.3%±39.7***	
		PT2567 0.1μM	94.5%±21.7	578.3%±23.9***	4,10%
		PT2567 1μM	96.2%±13.2	400.0%±57.8***	33.7% ^{##}
		PT2567 10μM	99.4%±8.1	522.4%±7.0***	13.4% [#]
	VEGF	DMSO	100.0%±30.9	516.0%±87.8***	
		PT2567 0.1μM	97.1%±20.6	384.4%±50.4***	25.5% [#]
		PT2567 1μM	114.8%±18.0	271.0%±54.0**	47.5% ^{###}
		PT2567 10μM	92.6%±20.9	276.0%±33.6**	46.5% ^{###}
Hypoxic induction of inflammatory genes in EC	CXCR4	DMSO	100.0%±15.0	350.0%±31.9**	
		PT2567 0.1μM	127.9%±26.3	319.3%±73.3**	8,77%
		PT2567 1μM	79.9%±1.01	85.9%±11.05	75.5% ^{##}
		PT2567 10μM	110.5%±18.0	98.2%±26.7	71.9% ^{##}
	ICAM1	DMSO	100.0%±33.1	450.8%±41.8**	
		PT2567 0.1μM	109.5%±60.0	105.6%±51.1	76.6% ^{##}
		PT2567 1μM	116.9%±35.4	115.9%±10.2	74.3% ^{##}
		PT2567 10μM	122.8%±15.5	143.2%±19.2	68.2% ^{##}
	SDF1	DMSO	100.0%±23.6	395.8%±18.3**	
		PT2567 0.1μM	184.6%±10.3	424.6%±1.02**	107,30%
		PT2567 1μM	59.0%±31.3	45.5%±133.3	88.5% ^{###}
		PT2567 10μM	99.1%±28.4	115.5%±4.74	70.8% ^{###}

Supplementary Table 8. Gene expression in EC by qRT-PCR, as in Fig. 7. Δ (inhibitory rate) refers how effective of HIF2 inhibitor PT2567 in reducing the induction of the gene by the hypoxia. Statistical significance as determined by t-test.

	Gene		Normoxia	Hypoxia	Δ
Hypoxic induction of signaling factors in EC	ID1	DMSO	100.0%±25.0	30.1%±4.3**	
		PT2567 0.1μM	107.5%±24.3	48.5%±10.1*	161,00%
		PT2567 1μM	134.5%±35.4	63.0%±3.3***	209.3% ^{##}
		PT2567 10μM	82.9%±0.53	69.4%±8.2	230.6% ^{##}
	ID3	DMSO	100.0%±4.6	57.8%±10.7**	
		PT2567 0.1μM	77.7%±31.2	63.7%±20.2	110,20%
		PT2567 1μM	89.4%±25.5	74.2%±12.6	128,40%
		PT2567 10μM	71.9%±10.05	77.3%±5.95	124,40%
	TGFA	DMSO	100.0%±46.4	384.7%±64.9***	
		PT2567 0.1μM	139.2%±22.04	180.7%±5.8***	53.02% ^{###}
		PT2567 1μM	147.6%±78.6	134.7%±3.1	65% ^{###}
		PT2567 10μM	185.5%±158.8	140.4%±10.5	63.5% ^{###}

Supplementary Table 8, continued.