Rat	CAGTTTTCAGAAACTGGGAAAAACTGAAATTGTTTGTCTCTTCTATGATCGATGATCACC
Human	$\tt CTCTCTTCAGCAACTGGAAAAACTGAAATTGTTTGTTTCTCATATGATTGACAAACACA$
246	TLFSNWKKLKLFVSHMIDKH
	ZEN target site in the rat
Rat	GGAAAGACTGGAACCCTGAGGAGCCAAGAGACTTCATTGATGCTTTCCTCAAGGAAATGT
Human	GAAAGGATTGGAATCCTGCAGAAACAAGAGACTTTATTGATGCTTACCTTAAAGAAATGT
266	RK-DWNPA-ETRDFIDAYLKEM
Rat	AAACAAAGTACCCAGAGAAGACTACAAGTTTCAATGAAGAAAACCTCATCTGCAGCACCC
Human	CAAAGCACACAGGCAATCCTACTTCAAGTTTCCATGAAGAAAACCTCATCTGCAGCACCC
286	SKHTGNPTSSFHEENLICST
Rat	TGGACCTCTTCTTTGCGGGAACAGAGACAACATCCACTACACTGCGCTGGGCTCTGCTCT
Human	TGGACCTCTTCTTTGCCGGAACCGAGACAACTTCCACAACTCTGCGATGGGCTCTGCTTT
306	LDLFFAGTETSTTLRWALL
	Ston gain in humans
Rat	ACATGGCCCTCTACGCAGAAGTGCAAGAAAAAGTACAGGCAGAGATTGACAGAGTCATTG
Human	ATATGGCCCTCTACCCAGAAATCCAAGAAAAAGTACAAGCTGAGATTGACAGAGTGATTG
326	YM-AI,YPEIOEKVOAEIDRVI
Det	
Ral	
540	G Q G Q Q F S I A A K E S M F I I N A V
	Premature stop codon
Rat	TCCATGAGGTGCAGAGGATGGGCAACATCATCCCCCCTGAATGTTCCCAGGGAAGTAGCAZ
Human	TCCATGAGGTGCAGAGAATGGGCAACATCATCCCCCTGAACGTTCCCAGGGAAGTGACAG
366	IHEVQRMGNIIPLNVPREVT
	Dutative home hinding site
_	
Rat	TTTTGGAGAATGGACAGTTTAAGAAGAGAGAATCTTTTCTGCCATTCTCAATGGGAAAGA
Human	TTCTGGAGAATGGACAGTTTAAGAAAAGGGAAGCCTTTATGCCTT
426	FLENGQFKKREAFMPFSIGK
1	Putative heme binding site
Rat	GAGCTTGCCTTGGAGAACAACTGGCCAGGTCTGAACTGTTCATTTTCTTCACTTCTCTT
Human	GGGCAMGCCTCGGAGACAGACCAGGACTGAGCCAGACTGAGTCCCCTT
446	
446	R-A-C-L-G-E-Q-L-A-R-T-E-L-F-I-F-I-F-T-S-L-
446	The sequence between 385 and 426 is not shown

25 bp deletion in the rat

В

Α



WT 361-420 YTNAVIHEVQRMGNIIPLNVPREVAMDTTLNGFHLPKGTMVLTNLTALHRDPKEWATPDV

Supplementary Figure 1. A. The comparative illustration of rat *Cyp2j4* and its human orthologue *CYP2J2* cDNA sequence and its corresponding peptide sequence in humans. The 25 bp deletion in the rat causes a premature stop codon upstream the putative heme binding site (residues 441, 444, 446, 448, 450 highlighted in grey). The frameshift deletion affects also the active site cavity identified in human CYP2J2 with residues I127, F310, A311, T315, I375, I376 and V380 (highlighted in grey) that are in close proximity to heme, providing a restricted access of substrates through a narrow hydrophobic channel (Lafite et *al.* Biochemistry 2007 11;46(36)). Note that human *CYP2J2* presents stop/gain mutations (identified by 1000 Genomes), one of them being 143 bp upstream the premature rat stop codon. **B**. The amino acid sequence of wild-type (WT) and *Cyp2j4⁻¹⁻* rat from 241-420 illustrating the frameshift caused at position 255. The frameshift sequence (shown in green colour) causes a stop codon at position 372.



Supplementary Figure 2. Expression levels of *Fn1*, *Col1a1*, *Col1a2*, *Col3a1* in primary fibroblasts derived from WT and $Cyp2j4^{-/-}$ skin (**A**) or lung (**B**) measured by qRT-PCR. Fibroblasts were cultured in either basal conditions or with addition of TGF β (10ng/ml for 48 hours). Note the marked expression differences between basal lung-derived WT vs $Cyp2j4^{-/-}$ fibroblasts for all the tested transcripts. n=3 rats/strain were used in four replicates and the results are representative of two independent experiments.



Supplementary Figure 3. A. Oxygen consumption rate (OCR) in WT and $Cyp2j4^{-/-}$ BMDMs measured by extracellular flux analyser in WT and $Cyp2j4^{-/-}$ BMDMs in basal conditions (assay medium) and in conditions were 11,12 EETs (1µM) were added onto $Cyp2j4^{-/-}$ BMDMs. OCR measurements were taken every 10min following addition of either basal or +11,12 EETs media for a total duration of 3h (See experimental procedures for details). The experiment was repeated three times with at least 4 technical replicates each time. *, P<0.001 when compared with WT; ns, non-significant when compared with WT. B. TNF α levels were quantified by sandwich ELISA in WT and $Cyp2j4^{-/-}$ BMDMs in basal (untreated) and lipopolysaccharide (LPS, 100ng/ml, 12h) treated samples. *, P<0.05 compared to WT (LPS) by nonparametric Wilcoxon signed-rank test; ns, non-significant when compared to WT (basal). The experiment was repeated four times using 4 biological replicates in duplicate.