

## Supplementary Materials

**Table S1.** Expression levels of transporter mRNA of selected genes in the liver of control and LPS-treated rats (24h after exposure to LPS).

ABC transporters						
Transporter (gene)	P-gp ( <i>Abcb1a/Mdr1a</i> )	P-gp ( <i>Abcb1b/Mdr1b</i> )	Mrp2 ( <i>Abcc2</i> )	Mrp3 ( <i>Abcc3</i> )	Mrp4 ( <i>Abcc4</i> )	
Healthy rats (n = 4)	2.9 ± 0.7	21.6 ± 3.4	129.6 ± 28.7	2.2 ± 0.9	2.7 ± 0.9	
LPS-treated rats (n = 4)	0.9 ± 0.4	5.4 ± 2.4	50.1 ± 20.9	0.8 ± 0.5	1.4 ± 0.6	
SLC transporters						
Transporter (gene)	Ntcp ( <i>Slc10a1</i> )	Oat2 ( <i>Slc22a7</i> )	Oatp1 ( <i>Slco1a1</i> )	Oatp2 ( <i>Slco1a4</i> )	Oatp4 ( <i>Slco1b2</i> )	Oct1 ( <i>Slc22a1</i> )
Healthy rats (n = 4)	248.0 ± 26.8	17.0 ± 2.9	74.4 ± 6.8	63.9 ± 8.9	193.5 ± 51.6	49.3 ± 8.6
LPS-treated rats (n = 4)	125.1 ± 17.6	18.7 ± 9.0	39.5 ± 9.8	10.9 ± 7.1	118.8 ± 53.8	22.9 ± 2.8
Cytochromes						
Cytochrome (gene)	Cyb2b1 ( <i>Cyp2b1</i> )	Cyp3a1 ( <i>Cyp3a23-3a1</i> )				
Healthy rats (n = 4)	0.4 ± 0.2	158.5 ± 26.7				
LPS-treated rats (n = 4)	0.2 ± 0.1	41.0 ± 8.3				

Values are in arbitrary units. (Abcb: ATP-binding cassette sub-family B, Abcc: ATP-binding cassette sub-family C, Cyp: cytochrome-P450, LPS: lipopolysaccharide, Mdr: multidrug resistance protein, Mrp: multidrug-resistance associated protein, Ntcp: Na<sup>+</sup>-taurocholate cotransporting polypeptide, Oat: organic anion transporter, Oatp: organic anion transporting polypeptide, Oct: organic cation transporter, Slc: Solute carrier family)

**Table S2.** Area under the time-activity curves (AUC) of <sup>99m</sup>Tc-mebrofenin in the blood pool (imaged-derived), liver and intestine obtained in all the studied rat groups.

Group	AUC <sub>blood</sub> (cps/MBq).min	AUC <sub>liver</sub> (cps/MBq).min	AUC <sub>intestine</sub> (cps/MBq).min
Healthy (n = 5)	51 ± 14	461 ± 109	425 ± 85
RIF 9 mg/kg (n = 5)	105 ± 23	559 ± 123	237 ± 55
RIF 40 mg/kg (n = 5)	109 ± 12	385 ± 28	223 ± 54
LPS (n = 6)	129 ± 57	814 ± 164	277 ± 65
LPS + RIF 9 mg/kg (n = 6)	159 ± 46	663 ± 188	202 ± 37
LPS + RIF 40 mg/kg (n = 6)	154 ± 70	564 ± 43	137 ± 60

Radioactivity is expressed in counts per second (cps) in each region of interest, normalized to the injected radioactivity amount in each animal (cps/MBq). Data are given as mean ± SD. (LPS: lipopolysaccharide, RIF: rifampicin). The data of healthy and RIF 40 mg/kg groups have already been presented in a previous study [29].

**Table S3.** Transfer rate constants obtained with the four-compartment model describing the hepatobiliary disposition of  $^{99m}\text{Tc}$ -mebrofenin in all the studied rat groups.

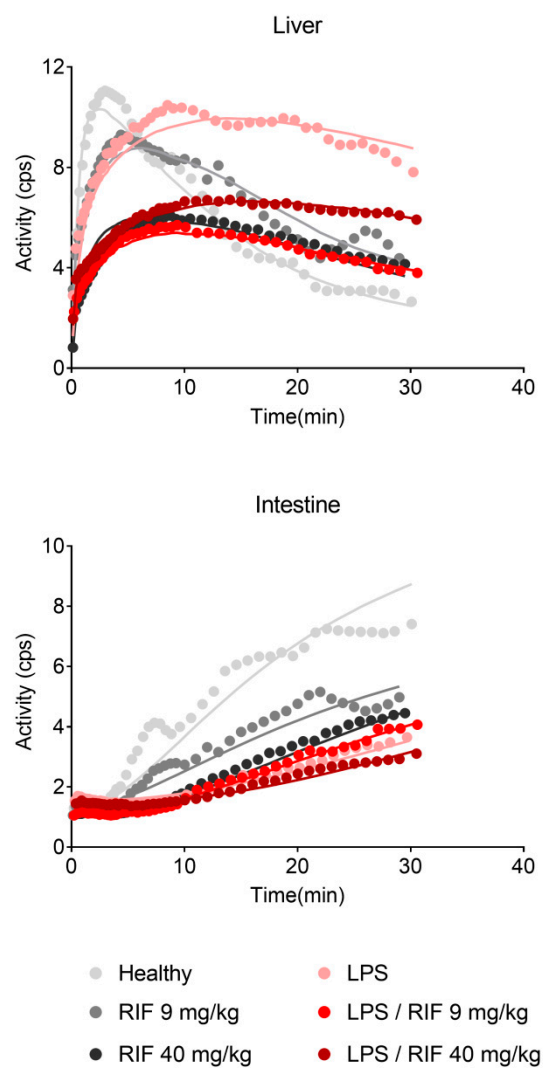
Group	$k_1$ (min $^{-1}$ )	$k_2$ (min $^{-1}$ )	$k_3$ (min $^{-1}$ )	$k_5$ (min $^{-1}$ )
<b>Healthy</b> (n = 5)	7.37 $\pm$ 1.62 (4.8 - 16)	0.15 $\pm$ 0.08 (7.2 - 30.8)	0.15 $\pm$ 0.08 (3.9 - 11.9)	0.12 $\pm$ 0.03 (2.4 - 12.5)
<b>RIF 9 mg/kg</b> (n = 5)	4.16 $\pm$ 1.43 (1.5 - 10.4)	0.04 $\pm$ 0.02 (4.0 - 17.6)	0.02 $\pm$ 0.01 (1.6 - 5.2)	1.04 $\pm$ 0.62 (17.0 - 53.2)
<b>RIF 40 mg/kg</b> (n = 5)	0.89 $\pm$ 0.09 (3.6 - 7.6)	0.01 $\pm$ 0.01 (28.7 - 125.7)	0.05 $\pm$ 0.02 (2.4 - 12.7)	0.64 $\pm$ 0.88 (13.6 - 31.7)
<b>LPS</b> (n = 6)	8.72 $\pm$ 3.37 (1.6 - 9.9)	0.07 $\pm$ 0.03 (2.9 - 17.8)	0.02 $\pm$ 0.01 (1.9 - 35.3)	0.30 $\pm$ 0.39 (9.8 - 49.3)
<b>LPS + RIF 9 mg/kg</b> (n = 6)	5.14 $\pm$ 3.05 (2.2 - 13.1)	0.08 $\pm$ 0.04 (4.0 - 19.4)	0.05 $\pm$ 0.02 (2.0 - 14.5)	0.08 $\pm$ 0.09 (6.6 - 19.4)
<b>LPS + RIF 40 mg/kg</b> (n = 6)	1.9 $\pm$ 0.78 (1.0 - 6.4)	0.03 $\pm$ 0.03 (7.2 - 39.9)	0.03 $\pm$ 0.01 (3.0 - 61.4)	0.10 $\pm$ 0.10 (14.7 - 69.9)

Values are given as mean  $\pm$  SD. Values in parentheses express percent coefficient of variation (%CV) of the parameters (parameter precision).  $k_1$  and  $k_2$  are the parameters describing the transfer of radiotracer between blood and liver compartments,  $k_3$  describes the radiotracer transfer from liver tissue to the intrahepatic bile ducts and  $k_5$  describes the transfer of radiotracer from the intrahepatic bile ducts to the intestines (excreted bile). The data of healthy and RIF 40 mg/kg groups have already been presented in a previous study [29].

**Table S4.** Primer sequences used for qPCR assays.

Gene (Protein)	Forward Primer (5'-3')	Reverse Primer (5'-3')
<i>Rn 18S</i>	CGCCGCTAGAGGTGAAATTC	TTGGCAAATGCTTTCGCTC
<i>Abcb1a/Mdr1a</i> (P-gp)	CAGGTTGGCTGGACAGATTT	CATGTCTCCAAAGACCAGCA
<i>Abcb1b/Mdr1b</i> (P-gp)	TTTGACTCGGGAGCAGAAGT	AAGGTGATCCCAAAGACGTG
<i>Abcc2</i> (Mrp2)	CGTCTCCTACGGTTTCCAGA	ACTCAGAAAGGAAGCCGTGA
<i>Abcc3</i> (Mrp3)	AGATCGCAGAGACAGGCAAT	CCAGCATACAGGAGGCAGAT
<i>Abcc4</i> (Mrp4)	TCAGATTGGTTATGAGGTCTG	CCATTCTGGTTATTCTGCTG
<i>Slc10a1</i> (Ntcp)	CAAGTCCAAAAGGCCACACT	TGATGACAGAGAGGGCTGTG
<i>Slc22a7</i> (Oat2)	CGCTCAGAATTCTCCTCCAC	GCACACCAATGAAGAAGCAG
<i>Slco1a1</i> (Oatp1)	AGGTCGAGAATGACGGAGAA	ATTCCGAGGAAGGGAAGTGT
<i>Slco1a4</i> (Oatp2)	TGGGATCTGTTTTCCACACA	ATCTCGCTACCCCACCATTTCT
<i>Slco1b2</i> (Oatp4)	GACATCACCCACTGGACCTT	AGCATGTTCCCATCAAGAC
<i>Slc22a1</i> (Oct1)	GGTTGCCAACAGGAGTCAGT	AGACAGAGCTTACGGCCAAA
<i>Cyp2b1</i> (Cyp2b1)	GGCTCACACCGGCTACCAA	TGAAAACCTCTGAATCTCGTGGATA
<i>Cyp3a23-3a1</i> ( <i>Cyp3a1</i> )	GTAAATACTTGAGGCAAGAGAAAG GC	TCGGGTTGTTGAGGGAATCA

(Abcb: ATP-binding cassette sub-family B, Abcc: ATP-binding cassette sub-family C, Cyp: cytochrome-P450, Mdr: multidrug resistance protein, Mrp: multidrug-resistance associated protein, Ntcp: Na $^{+}$ -taurocholate cotransporting polypeptide, Oat: organic anion transporter, Oatp: organic anion transporting polypeptide, Oct: organic cation transporter, Slc: Solute carrier family)



**Figure S1.** Time-activity curves of  $^{99m}\text{Tc}$ -mebrofenin in the liver and intestine for observed data (circles) and model fits (solid lines) in a representative subject of each studied rat group. (LPS: lipopolysaccharide, RIF: rifampicin). The data of healthy and RIF 40 mg/kg groups have already been presented in a previous study [29].