OATP1B1 and OATP1B3

Introduction:
Human OATP1B1 and OATP1B3 are highly expressed in liver, localized in the basolateral membrane of hepatocytes, where they mediates the uptake of many different drugs from blood into hepatocytes. OATP1B3 and OATP1B1 have a nearly consistent substrate spectrum. Compounds that are transported by OATP1B1 and OATP1B3 are estrone-3-sulfate (ES) and sulfobromophthalein (BSP) which are used as model substrates but also bile salts like taurocholate. Drug substrates of OATP1B1 and OATP1B3 are e.g. statins (pravastatin, rosuvastatin), antibiotics (rifampicin) and cytostatics (methotrexate). Inhibitors for both transporters are for example cyclosporineA, ketoconazole, MK571, ritonavir and paclitaxel.
For OATP1B1 and OATP1B3 regulatory agencies FDA and EMA decided that drugs eliminated via the liver has to be tested for drug-drug interaction, *in vitro*.

Methods: PortaCellTec Biosciences GmbH generated HEK293 cell lines stably expressing OATP1B1 or OATP1B3 transporter proteins and validated the cell-transporter system with reference substrates (^{3}H-estrone-3-sulfate for OATP1B1, ^{3}H-BSP (sulfobromophthalein) for OATP1B3) and different inhibitors. To perform uptake experiments, three days after cell seeding, the uptake was initiated by adding the reference substrate in the absence and presence of an inhibitor. To terminate the uptake cells were washed three times with cold assay buffer. The radio-labeled content (^{3}H or ^{14}C) of each cell lysates was analyzed by liquid scintillation counting.

OATP1B1 – SLCO1B1

Substrate	Inhibitor	Kinetic parameters	References
Estrone-3-sulfate (ES)	---	K_m = 0.25 µM	K_m = 0.2 µM (Tamai, 2000) K_m = 0.5 µM (Hirano, 2004)
Estrone-3-sulfate (ES)	Rifampicin	IC_{50} = 1.0 µM	K_i = 0.5 µM (Hirano, 2006) IC_{50} = 1.5 µM (Gui, 2008)

Figure 1 Concentration dependent OATP1B1 mediated net-uptake of ES

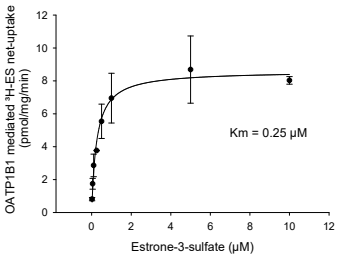
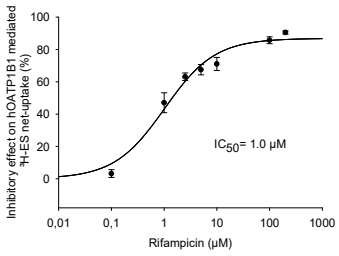


Figure 2 Inhibition of OATP1B1 mediated ES net-uptake by rifampicin



OATP1B3 – SLCO1B3

Substrate	Inhibitor	Kinetic parameters	References
BSP	---	K_m = 0.5 µM	K_m = 0.4 µM (Kullak-Ublick,2001) K_m = 3.3 µM (Cui, 2001)
BSP	Rifampicin	IC_{50} = 0.9 µM	IC_{50} = 1.5 µM (Letschert, 2006)

Figure 3 Concentration dependent OATP1B3 mediated net-uptake of BSP

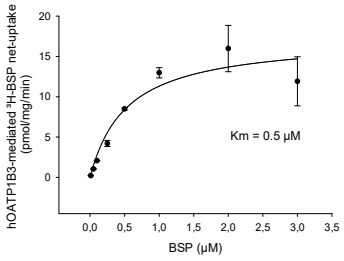
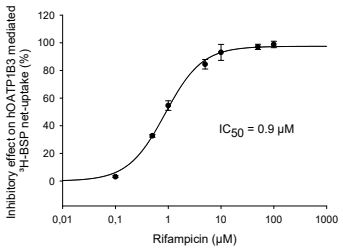


Figure 4 Inhibition of OATP1B3 mediated BSP net-uptake by rifampicin



PCT provides transporter interaction service for all following OATPs:

Protein	Gene	Expression	Substrates	Inhibitors
OATP1A2	SLCO1A2	brain, kidney, liver	estrone-3-sulfate, fexofenadine, trospium, ouabain, pitavastatin	rifampicin, verapamil, BSP, ritonavir, naringin, hesperidin
OATP1B1	SLCO1B1	liver	estrone-3-sulfate, pravastatin, BSP, rosuvastatin, rifampicin, methotrexate	rifampicin, cyclosporineA, ketoconazole, MK571, ritonavir, paclitaxel
OATP1B3	SLCO1B3	liver	BSP, CCK8, fluvastatin, pravastatin, pitavastatin, methotrexate, rifampicin	rifampicin, cyclosporineA, ketoconazole, MK571, ritonavir, paclitaxel
OATP2A1	SLCO2A1	kidney, lung, intestine, eye	prostaglandine	diclofenac, lumiracoxib
OATP2B1	SLCO2B1	liver, placenta, intestine	estrone-3-sulfate, fexofenadine, BSP, pitavastatin, fluvastatin, taurocholate	rifampicin, cyclosporinA, MK571, ketoconazole, glibenclamid, ritonavir

Literatur

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