ABC-Transporters: BCRP and BSEP

Vesicle-based transporter assay for BCRP (ABCG2) and BSEP (ABCB11)

Membrane vesicles (inside-out orientated) prepared from single stably transfected BCRP-HEK respective BSEP-HEK and control-HEK vesicles are used to measure the ATP-dependent direct uptake of a radio-labeled probe substrate in the absence and presence of a probe inhibitor by rapid filtration method. Vesicles are best suited for low permeability substrates because of poor retention of moderate-to high permeability compounds. In vitro inhibition studies are recommended by FDA and EMA to investigate whether the investigational drug inhibits any of the efflux transporters BCRP, BSEP and MDR1 which are known to be involved in clinically relevant in vivo drug interaction.

BCRP- ABCG2

BCRP-HEK Vesicles	Kinetic Parameters	References
Estrone-3-sulfate (ES) (Substrate)	Km = 6.3 µM	Km = 6.8 µM (Imai, 2003), Km = 11 µM (Anderson, 2010)
GF120918 (Inhibitor)	IC_{50}= 0.39 µM	IC_{50} =0.31 µM (Ahmed-Belkacem, 2005)
Sulfasalazine (Inhibitor)	IC_{50}= 0.27 µM	IC_{50} = 0.73 µM (Elsby, 2011)
Ko143 (Inhibitor)	IC_{50}= 0.15 µM	IC_{50} =0.02 µM (Allen, 2002)

Figure 1 Concentration dependent BCRP-mediated net-uptake of ^{3}H-Estrone-3-sulfate

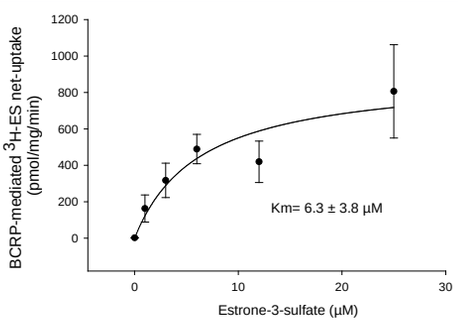


Figure 2 IC_{50} determination of BCRP-mediated ^{3}H-Estrone-3-sulfate net uptake by GF120918

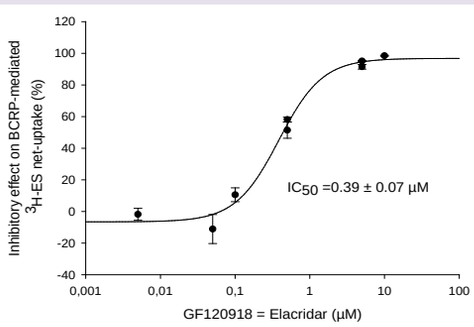
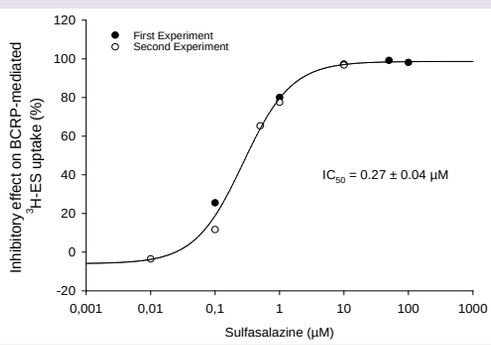


Figure 3 IC_{50} determination of BCRP-mediated ^{3}H-Estrone-3-sulfate net-uptake by sulfasalazine



BSEP- ABCB11

BSEP-HEK Vesicles	Kinetic Parameters	References
Taurocholate (TA) (Substrate)	Km = 11 µM	Km = 4.64 µM (Hirano, 2005)
CyclosporinA (Inhibitor)	IC_{50} = 1.2 µM	IC_{50} = 8.4 µM (Kis, 2009)
Glibenclamide (Inhibitor)	IC_{50} = 5.2 µM	Ki = 27 µM (Byrne, 2002)

Figure 4 Concentration dependent BSEP-mediated uptake of ^{3}H-Taurocholate

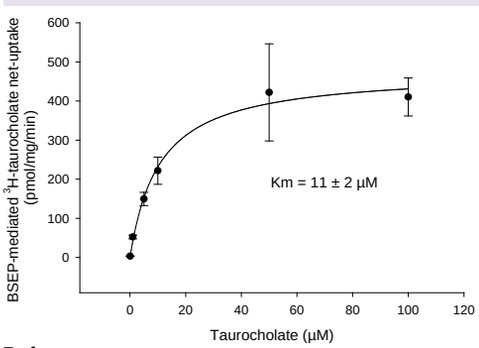


Figure 5 IC_{50} determination of BSEP-mediated ^{3}H-Taurocholate uptake by cyclosporineA.

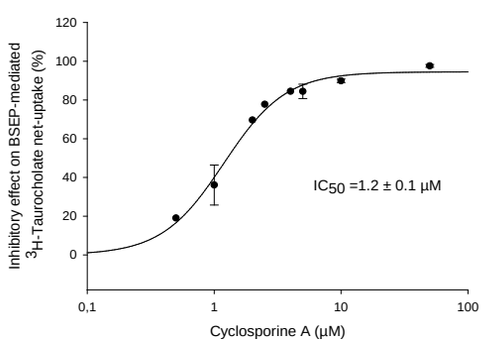
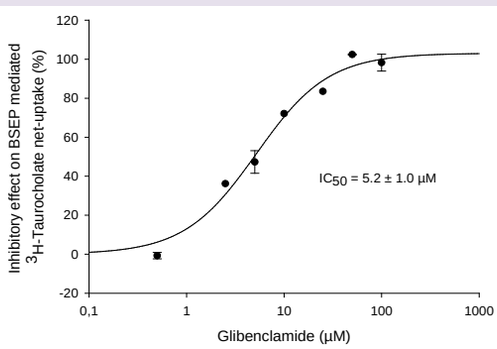


Figure 6 IC_{50} determination of BSEP-mediated ^{3}H-Taurocholate uptake by glibenclamide.



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