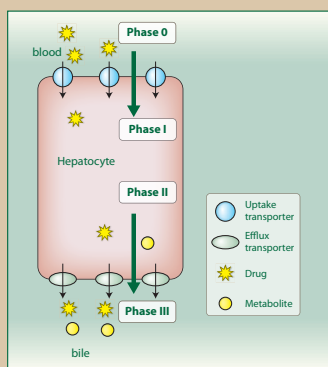


# PREDISCREEN LIVER package

complex *in vitro* & *in vivo* tool to investigate drug hepatic transporter interactions

The screening of the interaction of test drugs, nutrients and other molecules with hepatic efflux and uptake transporters is an indispensable aspect to study their hepatobiliary DMPK.

To gain information on biliary clearance, BSEP (ABCB11), MRP2 (ABCC2), BCRP (ABCG2) and MDR1 (ABCB1/P-gp) transporter interactions need to be investigated. For the detection of possible interactions on the basolateral membrane MRP3 (ABCC3), MRP4 (ABCC4) and MRP5 (ABCC5) efflux transporters should be considered. The involvement of human uptake transporters in the hepatic transport processes is just as crucial as the role of the efflux transporters. When investigating hepatobiliary disposition, it is highly recommended to perform studies for NTCP, OATP-C (OATP2 / OATP1B1), OATP8 (OATP1B3), OATP-B (OATP2B3), OAT2 and OCT1. In case of rat pharmacokinetic studies rat Ntcp, rat Oatp1 (Oatp1a1), rat Oatp2 (Oatp1a4), rat Oatp4 (Oatp1b2), rat Oat2 and rat Oct1 uptake transporters should be considered.



The three major questions that can be addressed by *in vitro* & *in vivo* transporter tools in hepatobiliary pharmacokinetics are:

1. Do non-membrane permeable drugs get into hepatocytes via active uptake transport processes?
2. Do drugs or their metabolites get excreted into the bile by canalicular efflux or removed by sinusoidal efflux?
3. Can drug-drug interactions or interactions with endogenous transporter substrates be expected resulting in liver toxicity or other adverse effects?

Fig 1: Interplay between Uptake transporters, Metabolic enzymes and Efflux transporters

## AVAILABLE ASSAYS WITHIN SOLVO LIVER PACKAGE

### Membrane based HTS efflux transporter assays:

- MDR1-PREDEASY ATPase
- ratMdr1b-PREDEASY ATPase
- MRP2-PREDEASY ATPase, ratMrp2-ATPase
- BCRP-HAM-PREDEASY
- mouseBsep-PREDEASY ATPase
- MRP3-PREDEASY ATPase
- MDR1- PREDIVEZ-VT
- ratMdr1b-PREDIVEZ-VT
- MRP2-PREDIVEZ-VT
- BCRP-M-PREDIVEZ-VT
- BSEP-VT, mouseBsep-VT
- MRP3- PREDIVEZ-VT
- MRP5- PREDIVEZ-VT

### Whole cell based HTS transporter assays:

- MDR1 Calcein Assay, BCRP Hoechst Assay
- OATP1B1, OATP1B3, OATP2B1 and ratOatp1a1
- NTCP, ratNtcp
- OCT1

### Monolayer assays:

- Double transfected cells (OATP-B / BCRP)
- MDCKII BCRP AB/BA transport
- MDCKII mouseBcrp1 AB/BA transport

### Rat *in vivo* liver studies including functional testing of ratMrp2, ratBsep and ratBcrp transporters

***In vivo* assays:** *In vivo* biliary efflux experiments are performed on male Wistar rats kept under standard laboratory conditions. All procedures are approved by the Institutional Animal Care and Use Committee. Tracer doses of <sup>3</sup>H-Estradiol-17- $\beta$ -D-glucuronide, <sup>3</sup>H-Taurocholate, <sup>3</sup>H-Estrone-3-sulfate, probe substrates for Mrp2, Bsep and Bcrp, respectively are coadministered with the test compounds i.p. Control rats receive the probe substrates and the vehicle only. Bile samples are collected, weighted and analyzed by liquid scintillation. Interactions with the transport proteins are determined from the altered biliary elimination of the probe substrates. A representation of the assay is shown in Figure 2/C.

