

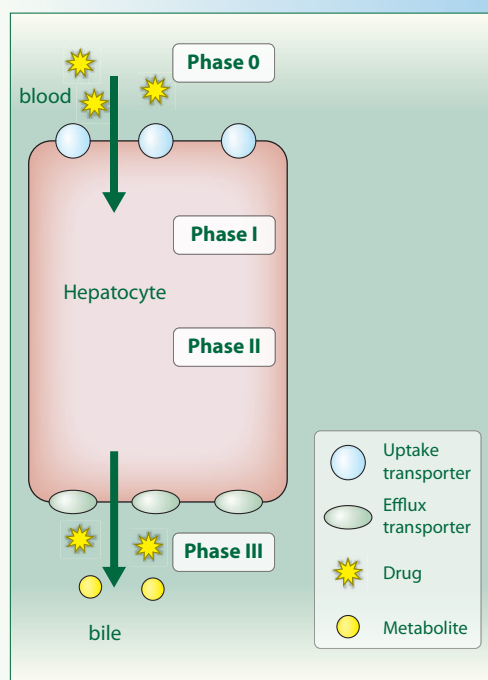
SOLVO TRANSFECTED MONOLAYERS FOR VECTORIAL TRANSPORT

SOLVO Biotechnology extended its PREDISCREEN™ portfolio with OATP-B (OATP2B1)/BCRP (MXR, ABCG2) double transfected cell line packages

Monolayer systems consist of a tight cell layer grown on a porous support to separate two fluid compartments. They are widely regarded as the most sophisticated in vitro tools for medium to high throughput modelling of important pharmacokinetic barriers such as intestinal epithelium, blood-brain barrier etc (see Hamilton RD et al. 2007. for a recent application). Monolayers based on Caco-2 cells (a human colon carcinoma cell line) have become an industry standard for the investigation of intestinal absorption (Oh DM et al. 2002.).

Differentiated Caco-2 cells express a wide range of transporter proteins on its cell membranes (Siissalo S et al. 2007.) similar to those of intestinal endothelium cells (Calcagno AM et al. 2006.). This makes Caco-2 cells ideal for intestinal absorption simulations, but limits the utilization of the cell line in the exploration of active processes through barriers. Since transporters can have major effects on the pharmacokinetics of drugs, there is an increasing need to look at interactions on individual transporters.

The development of transporter transfected cell lines that form tight cell layers brought about the possibility of investigating single transporter interactions on monolayers. MDCKII and LLC-PK1 cell lines, both kidney epithelium derived, have been widely used as hosts. The difference between efflux ratios on the transfected and parental cell lines is regarded as a sign of transporter mediated active uptake or efflux process. Introduction of double transfected cell lines, where an apical efflux transporter is located opposite a basolateral uptake transporter with overlapping substrate specificities, allowed the efficient vectorial transport of substrates and thereby experiments on low passive permeability molecules (Sasaki M et al. 2004., Mita S et al. 2005., Sasaki M et al. 2002., Lui L et al. 2006., Letschert K et al. 2005., Cui Y et al. 2001.). A schematic representation of the vectorial transport is shown in the figure.



Adapted from Kim 2002 Toxicology 181-2:291

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SOLVO Biotechnology introduces the PREDISCREEN™ OATP-B (OATP2B1)/BCRP (MXR, ABCG2) double transfected cell line based monolayer package. This package contains two single transfectants and the parental cell lines that are applied as controls

BCRP (MXR, ABCG2)

BCRP is one of the most important efflux transporters in endothelial and epithelial cells, modulating ADME properties of drugs (reviewed in Mao and Unadkat, 2005). It is a half-transporter that works as a homodimer (Ozvegy et al., 2001; Kage et al., 2002). ABCG2 has broad substrate specificity as it transports hydrophobic, anionic and cationic drugs (Mao and Unadkat, 2005). It is widely believed that ABCG2 plays an important role in intestinal absorption (Polli et al., 2004), secretion of xenobiotics and metabolites (Ebert et al., 2005), secretion of sulphate conjugates in the liver (Zamek-Gliszczynski et al. 2006) and prevention of penetration of drugs into the brain (Breedveld et al., 2005) or fetal tissues through the placenta (Jonker et al., 2000). ABCG2 knock-out models shed light on some special functions of ABCG2, such as secretion of drugs and other xenobiotics into the milk (Jonker et al., 2005) and protection of stem cells from hypoxia-induced protoporphyrin accumulation and damage (Krishnamurthy and Schuetz, 2005).

OATP-B (OAT2B1)

OATP-B is a sodium independent uptake transporter expressed most prominently in the basolateral membrane of hepatocytes (Tamai I et al. 2000.). Its presence in the placenta and the ciliary body has also been shown (St-Pierre MV et al. 2002.). The main assigned physiological role of OATP-B is the uptake of several steroid derivatives (e.g. estrone-3-sulfate, dehydro-epiandrosterone-sulfate etc.) and other organic anions into hepatocytes (Kullak-Ublick et al. 2001.). The transporter also pumps several anionic drugs (e.g. fexofenadine, rifampin, ticlopidine, fluvastatin etc.) thereby influencing drug pharmacokinetics (Noé J et al. 2007., Lu WJ et al. 2006., Shimizu M et al. 2005.).

SOLVO new PrediScreen™ services

SOLVO new PrediScreen products apply **MDCKII cell lines transfected with both BCRP and OATP-B**. This combination models vectorial transport across hepatocytes as well as endothelial cells in the placenta. (Grube M et al. 2007., Grube M et al. 2006.). **The single transfectants and the parental cell lines provide negative controls for the transport.** SOLVO offers two setup groups, one for direct measurements and one for indirect inhibitory type measurements where the effect of test articles on the vectorial transport of a reference substrate can be examined. **SOLVO also presents direct and indirect setups for BCRP and mouse Bcrp1 interactions on single transfectant cell lines for medium to high permeability test articles.** The following tables and graphs summarize the details of these newly launched services.

