

# UPTAKE TRANSPORTERS

## Services, Products and Licensing

Uptake transporters play a key role in the pharmacokinetic profile of many structurally unrelated drugs. Present at all important pharmacological barrier tissues these proteins enable the translocation of medium to low permeability drug substances across plasma membranes and thereby determine absorption, distribution and elimination routing. Testing for interactions with uptake transporters has the potential to predict the main factors in the system level movement of drugs.

Assessing the inhibitory potential of test articles on uptake transporters may indicate drug-drug interaction implications, such as in the case of cyclosporin A and statins (1, 2). Today, combination therapies are widely used for drugs of many different therapeutic classes. Statins are often co-medicated with other drugs like immuno-suppressants, antidiabetic drugs or fibrates to treat patients in clinics. This increases the risk for significant DDIs amongst these drugs (3, 4, 5, 6). Therefore, it is important to address possible DDI risks relevant for the respective patient population by using appropriate *in vitro* tools to guide tailor-made clinical interaction studies in drug development. In addition to the well established cytochrome P450 interaction studies, DDIs can also occur at the level of active drug transport, involving OATP and OAT carriers and/or different ABC transporters. In the context of DDIs

involving statins, members of the OATP solute carrier family were found to be involved in addition to cytochrome P450 enzymes. Recombinant cell-lines expressing human OATP carriers are often used to study the *in vitro* DDI potential at the level of these carriers (7).

### References:

1. Shitara Y, Itoh T, Sato H, Li AP and Sugiyama Y (2003) J Pharm Exp Ther 304:610-616
2. Shitara Y, Horie T and Sugiyama Y (2006) Eur J Pharm Sci 27:425-446
3. Backman JT, Kyrklund C, Neuvonen M and Neuvonen PJ (2002) Clin Pharmacol Ther 72:685-691.
4. Hodel C (2002) Toxicol Lett 128:159-168.
5. Williams D and Feely J (2002) Clin Pharmacokinet 41:343-370.
6. Campbell SD, de Morais SM and Xu JJ (2004) Chem Biol Interact 150:179-187.
7. Hirano M, Maeda K, Shitara Y and Sugiyama Y (2006) Drug Metab Dispos 34:1229-1236.

**SOLVO Biotechnology has developed a wide range of stably transfected cell lines for studying the interaction of test articles with uptake transporters.**

**Services, ready-to-use products and licensing of cell lines are available.**

### AVAILABILITY

Uptake transporter assays are available for the following transporters:

Transporter	Cell type	Service	PREDICELL™	Licence
<b>OATP1B1</b> (SLCO1B1) / OATP2, OATP-C)	CHO	✓	ⓘ	ⓘ
<b>OATP1B3</b> (SLCO1B3 / OATP8)	CHO	✓	ⓘ	ⓘ
<b>OATP2B1</b> (SLCO2B1 / OATP-B)	MDCKII	✓	ⓘ	✓
<b>ratOatp1a1</b> (Slco1a1)	CHO	✓	ⓘ	ⓘ
<b>NTCP</b> (SLC10A1)	CHO	✓	ⓘ	ⓘ
<b>ratNtcp</b> (Slc10a1)	CHO	✓	ⓘ	ⓘ
<b>PEPT1</b> (SLC15A1)	CHO	✓	ⓘ	✓
<b>PEPT2</b> (SLC15A2)	CHO	✓	ⓘ	✓
<b>OAT1</b> (SLC22A6)	CHO	✓	✓	✓
<b>OAT3</b> (SLC22A8)	CHO	✓	ⓘ	✓
<b>OCT1</b> (SLC22A1)	CHO	✓	ⓘ	✓
<b>OCT2</b> (SLC22A2)	CHO	✓	✓	✓

**SOLVO'S uptake transporter portfolio is continuously expanding.**

ⓘ Please, check our website ([www.solvo.com](http://www.solvo.com)) or call us for more information .

**Custom development of other transfected cell lines is also available from SOLVO.**

## SERVICES

SOLVO provides two types of uptake transporter studies: (i) inhibition assessment, and (ii) substrate assessment. Both are suitable for DDI studies: the indirect assays use predefined uptake transporter substrates for this purpose, while the direct assays can be designed to test the drug-drug interaction of the client's Test Article (TA) with any potential perpetrator compound.

The indirect and direct uptake transporter assays are performed with stable transfectants expressing selected human or rat uptake transporters. Cells adhere to treated surfaces which allow the easy separation of transported and excess low permeability substrate molecules.

### Inhibitor assessment studies

In these assays the inhibitory potential of the TA on the uptake transporter-mediated transport of a labelled probe substrate is measured (see a sample measurement in Fig. 1). The assay is performed with cold TA. The probe substrate is transported into the transfected cells by the selected human uptake transporter. Values are presented on a relative scale with 100% defined as transport in the presence of the solvent and without TA (no inhibition), and 0% defined as transport detected without transporter activity.  $IC_{50}$  is defined as the concentration required to inhibit the transport of the reporter substrate by 50%. This assay provides information on any interaction (sub-

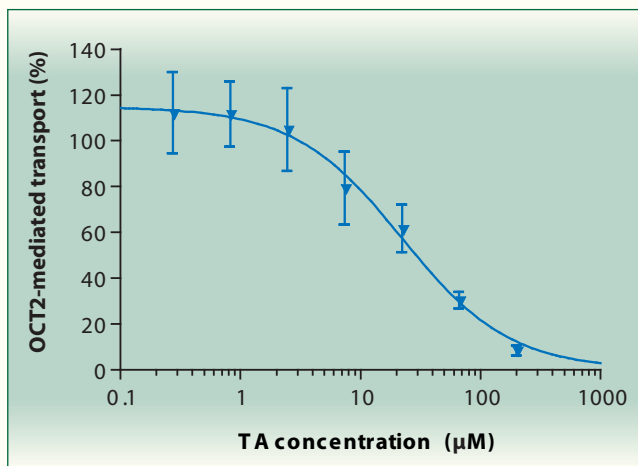


Figure 1: Inhibition of OCT2-mediated uptake of  $^{14}C$ -TEA by the Test Article

strate or inhibitor) between selected uptake transporters and the investigated TA that would affect the transport of the probe substrate. This assay does not give information on the nature of the interaction (transported substrate or inhibitor).

### Substrate assessment studies

Substrate assessment is usually performed as a follow-up on an inhibition study, but can be performed separately

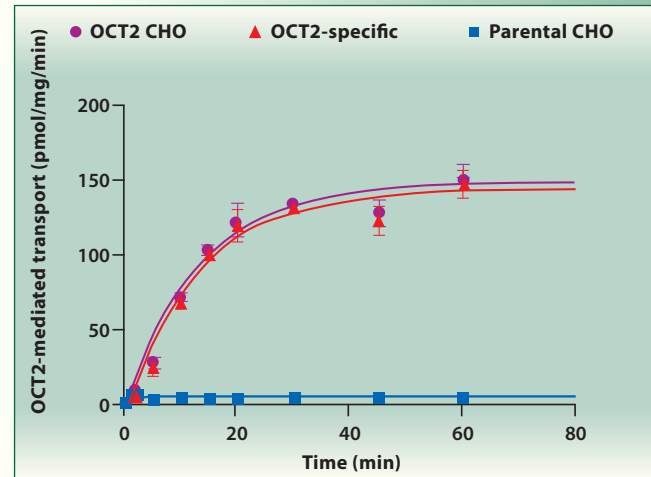


Figure 3/A: Time dependence of OCT2-mediated TA uptake

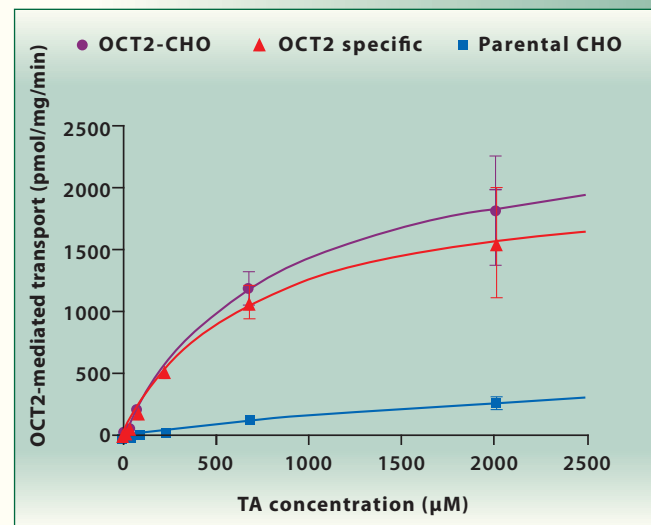


Figure 3/B: Concentration dependence of TA uptake into parental and OCT2 expressing CHO cells.

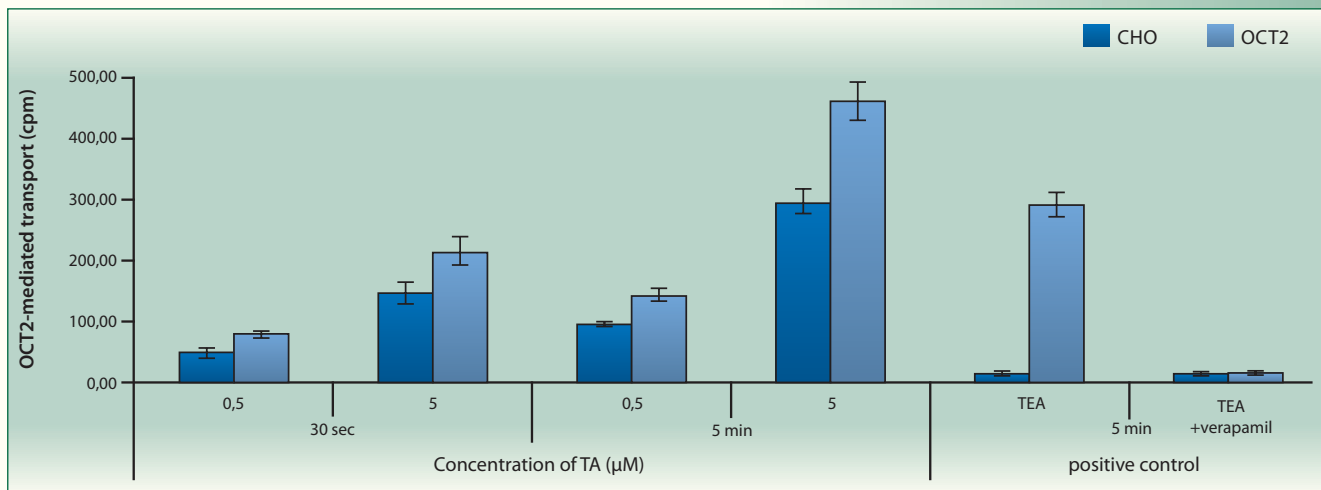


Figure 2: Accumulation of the Test Article in human OCT2-transfected CHO cells and in control cells measured in the direct uptake transporter assay





### **CONTACT INFORMATION:**

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