Solutions by SOLVO to support your ADME-Tox research

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Business Development Manager

SOLVO Biotechnology | A Charles River Company

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Who is SOLVO?

1999
SOLVO
The first transporter CRO

2012
Boston
Office

2015
Seattle
Office

2017
San
Francisco
Office

2018
Joined
Citoxlab Group

2019
Joined
Charles
River

About SOLVO
– The Transporter Company

- ~100 employees, of which 60 scientists - 20 in R&D
- Over 500 clients worldwide, from Virtual Companies to Big Pharma
- 2 main facilities, beside small US offices:

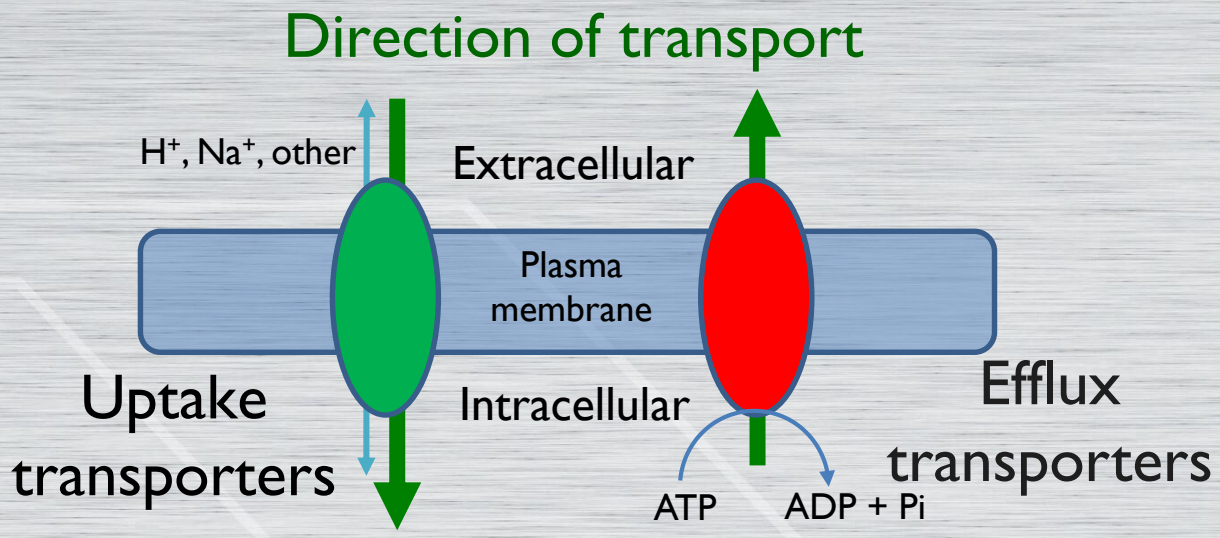
Budapest, Capital, Central Hungary

Research and Development lab
Automation lab
Contract Research Services, incl. on-site bioanalytics
Business Development

Szeged, South Hungary

Contract Research Services lab, incl. on-site bioanalytics
Production lab
Metabolism lab
Backoffice

Types of Transporters



- Cell membrane forms hydrophobic barrier limiting passive diffusion of non-lipophilic molecules
- Transporters required to move these substances into (uptake) or out of (efflux) cells
- Estimated 10% of human genome transporter-related

(~2,000 genes; Hediger et al., 2013 Mol. Aspects. Med.)

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Uptake (SLC) transporters

Mediate active transport of compounds accross cell membranes

Energy source differs per family of transporters (sodium gradient, proton gradient, etc)

Transport wide variety of molecules: peptides, organic anions and cations, bile acids, amino acids, fatty acids, etc.

OATPs, OATs, OCTs, OCTNs, MATE, etc

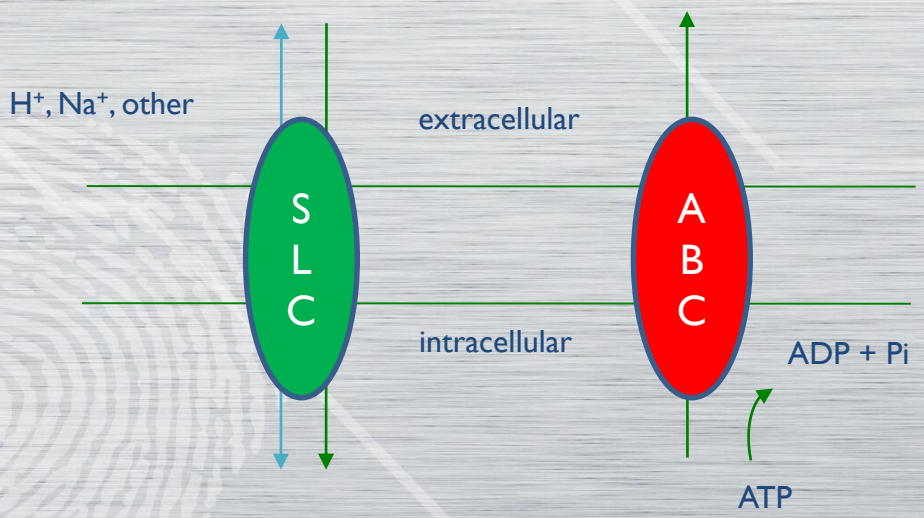
Efflux (ABC) transporters

>1,000 different transporters in the family (49 human)

Energy source: ATP

Alter pharmacokinetics of drugs, nutrients and other molecules

MDR1 (P-gp), BCRP, MRPs, BSEP etc



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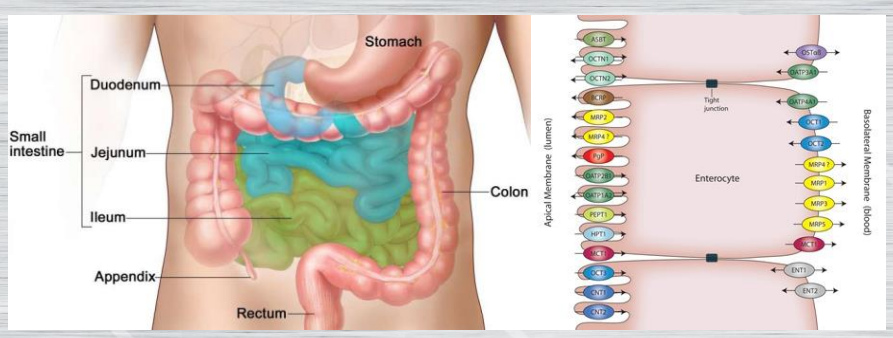
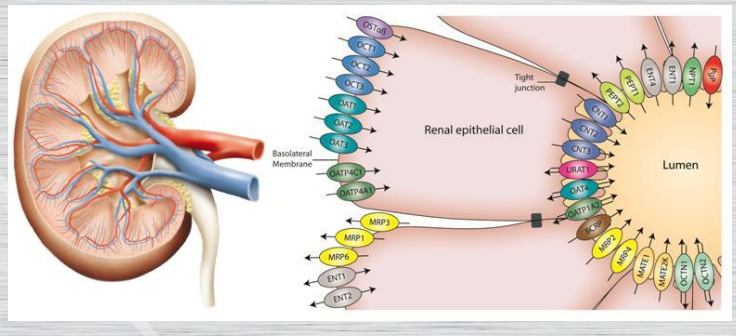
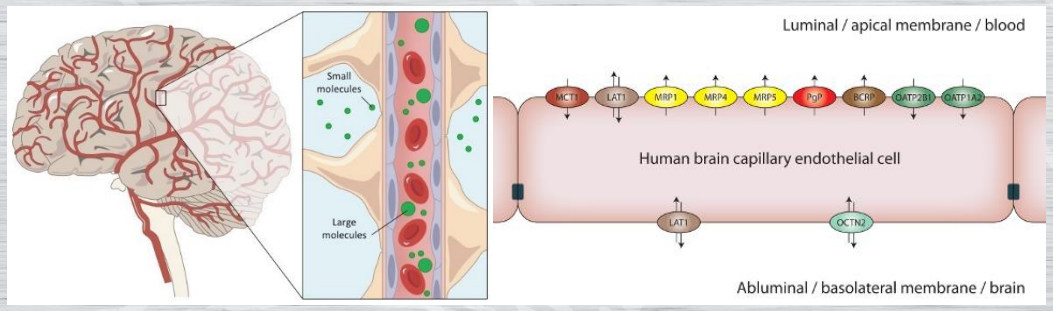
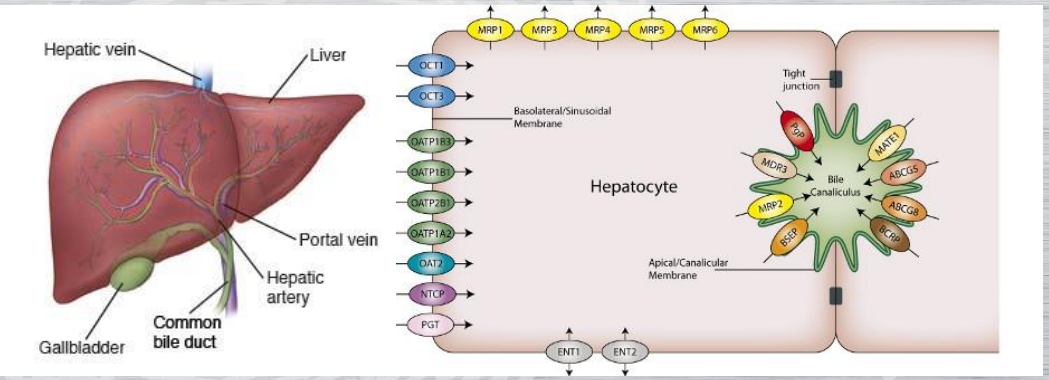
Transporters in ADMETox

Crossing barriers → Interaction with transporters → -Efficacy -Side effects - Toxicity - DDIs









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- Transporters can limit tissue distribution
  - regulation of entry/accumulation to/in CNS by MDR1
- Transporters can mediate drug clearance
  - Penicillin G too rapid renal elimination
  - + Probenecid $\Rightarrow$ 3.3 fold increase
- Effect on tissue may not show in plasma
  - Metformin (type2 diabetes)
  - Site of action: liver
  - Excreted in urine (OCTs, MATEs)
  - OCT1 (-/-) mice: no metformin plasma AUC change
  - While ~90% reduction in liver distribution
- Transporters as targets
  - Sodium-glucose cotransporters, Uric acid transporter
- Multiple transporters shown to mediate clinical DDIs
- Natural product-drug interactions

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When to study transporters?

- **Disc**overy to **F**irst **T**ime **I**n **H**uman

  Clinical Strategy

  therapeutic area, comedications, product profile, development plan, physicochemical properties
- **F**irst **T**ime **I**n **H**uman to **P**roof **O**f **C**oncept

  Understanding

  Non-clinical in vitro and in vivo studies

  Clinical studies for farmacokinetics, safety
- **P**roof **O**f **C**oncept to **N**ew **D**rug **A**pplication / **Market**ing

  Translation

  Drug labeling, Non-clinical mechanistic or investigative studies

  Clinical studies

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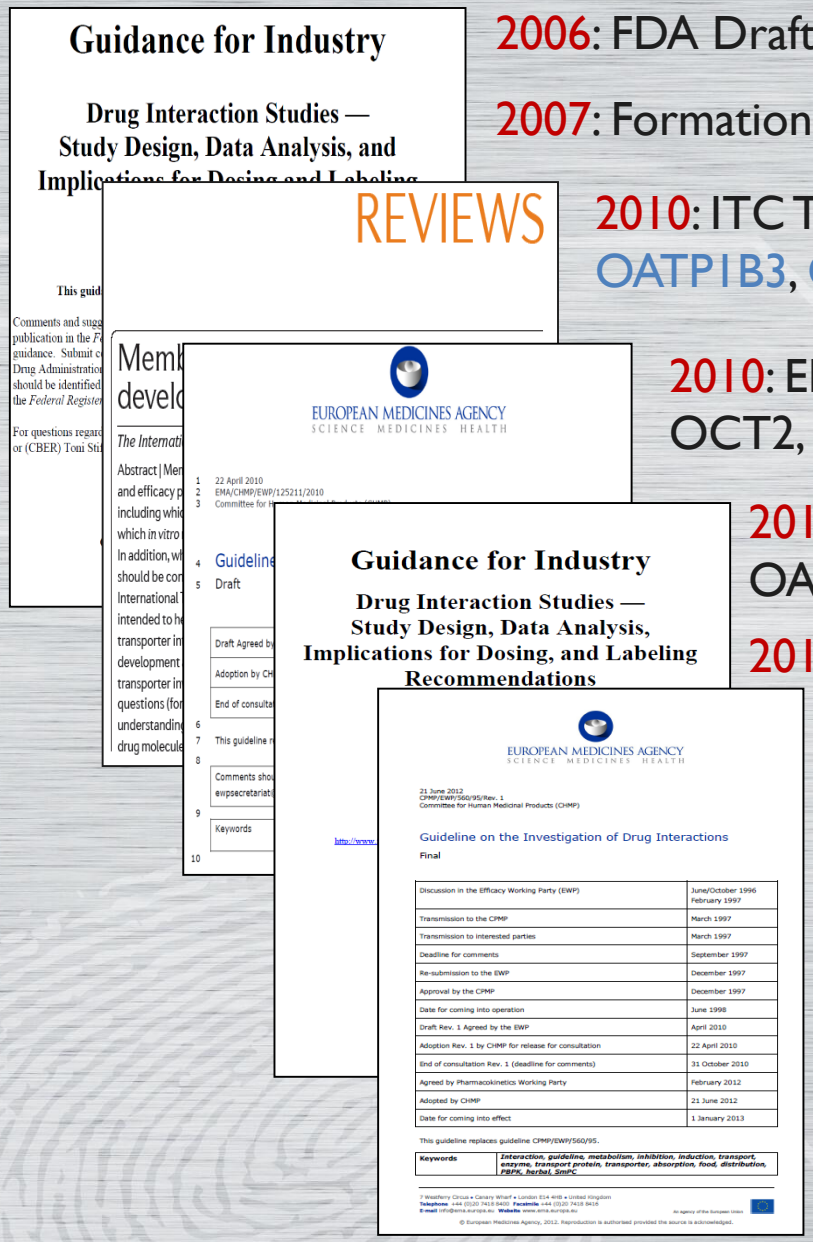
Regulatory aspects



2006: FDA Draft Guidance (P-gp)

2007: Formation of International Transporter Consortium (ITC)

2010: ITC Transporter White Paper (P-gp, BCRP, OATP1B1, OATP1B3, OCT2, OAT1, OAT3)

2010: EMA Draft Guidance (P-gp, BCRP, OATP1B1, OATP1B3, OCT2, OAT1, OAT3, BSEP, OCT1)

2012: Revised FDA Draft Guidance (P-gp, BCRP, OATP1B1 OATP1B3, OCT2, OAT1, OAT3, BSEP, MATEs, MRPs)

2013: Seven ITC Whitepapers Published

2013: Final EMA Guidance (more detailed)

2014: PMDA Guidance published

2017: PMDA Draft Guidance Updated

2017: EMA Concept Paper on Guidance Update Released

2017: Revised FDA Draft Guidance Released

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Latest FDA Draft guidance
Oct 2017

- 1. MATE1 and MATE2-K to be studied
- 2. (Time Dependent Inhibition) Potentiation of Transporter Inhibition by Preincubation
- 3. Calibration of in vitro systems – generate cut-off values for inhibition studies
- 4. More emphasis on study design:
  - Solubility limits
  - Non-specific binding
  - Probe substrate concentrations - below K_M
  - Choice of probe substrate

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Current Regulatory Requirements

		INHIBITION STUDIES		SUBSTRATE STUDIES	
	Transporter	EMA	FDA	EMA	FDA
EFFLUX	P-gp	yes	yes	consider	yes
	BCRP	yes	yes	consider	yes
	BSEP	prefer	no	consider	no
	MRPs	no	no	consider	no
UPTAKE	OAT1	yes	yes	consider	≥25% of elimination is active renal
	OAT3	yes	yes	consider	
	OATP1B1	yes	yes	≥25% of elimination hepatic	≥25% of elim. hepatic or biliary
	OATP1B3	yes	yes		
	OCT1	consider	no	consider	no
	OCT2	yes	yes	consider	≥25% of elimination is active renal
	MATE1	consider	yes	consider	
	MATE2-K	consider	yes	consider	

	Assay	EMA	FDA
Supportive	Solubility	yes	yes
	Non-specific binding	yes	yes

- Supportive experiments should be included as well
- Core panel of transporters but other transporters to be considered
- BSEP: role in hepatotoxicity (cholestasis/DILI), while limited role in biliary clearance
- OCT: interactions exist *in vitro*, but to date no clinical DDI can be attributed solely to OCT1
- **Tailored study design supported by expert scientists to fit best to the actual needs**
- **Importance of scientific discussion!**

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Appendix of guidance

- FDA 2017 guidance describes technical details of test systems and considerations.
- All SOLVO assays are compatible, and take these considerations into account

Table 1. Examples of In Vitro Systems to Investigate Transporter-Mediated Drug Interactions

Transporter	In Vitro Systems
ABC Transporters	
BCRP, P-gp	Caco-2 cells, commercial or in-house membrane vesicles, knock-out/down cells, transfected cells (MDCK, LLC-PK_1, etc.)
Solute Carrier (SLC) Transporters	
OATPs	Hepatocytes, transfected cells (CHO, HEK293, MDCK, etc.)
OATs, OCTs	Transfected cells (CHO, HEK293, MDCK, etc.)
MATEs*	Commercial or in-house membrane vesicles, transfected cells (CHO, HEK293, MDCK)

CHO: Chinese hamster ovary cell
HEK293: human embryonic kidney 293 cell
LLC-PK1: Lewis-lung cancer porcine kidney 1 cell
MDCK: Madin-Darby canine kidney cell

*The function of MATEs depends on the driving force from oppositely directed proton gradient; therefore, the appropriate pH of MATE assay system should be employed.

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What does SOLVO offer?

SOLVO is a leading provider of products and services for *in vitro* testing of transporter, metabolism and mechanistical toxicology studies.

Discovery

- Custom transporter assays development
- Permeability studies
- Metabolism
- Transporters to target specific tissues

Safety

- Regulatory DDI studies
- Transporters in drug disposition
- Transporters in toxicity
- Holistic models for toxicity testing

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>200 Transporter Products and Services

- Efflux transporter services
- Uptake transporter assays
- Custom assay development
- LC/MS-MS quantification of transporter proteins
- qPCR gene expression analysis
- Drug metabolism services
- LC/MS-MS analytics
- Aqueous solubility services
- Protein binding/Non-specific binding
- Rat brain endothelial cell monolayer assay
- Caco-2 and KO monolayer assay
- Hepatocyte uptake , sandwich-culture (B-CLEAR™), and micropatterned co-culture (HepatoPac™) assays
- aProximate™ renal proximal tubule cell assay

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Snapshot of SOLVO's portfolio

	Individual Transporters		Cellular Barrier Models
	Human	Other species	
Liver	OATPs, MRPs, BSEP, NTCP, OCT1, MDR1, BCRP	Rat: Oatps, Mdr1a, Bcrp and Mrps, Bsep Mouse: mBcrp1, mBsep Cyno-monkey: Oatps and Ntcp	Hepatocyte uptake assay, B-CLEAR® HepatoPac®
Kidney	OATs, OCTs, MATEs, MRPs, MDR1, BCRP	Rat: Mdr1a, Bcrp1, rOat1, rOctn2 Mouse: mBcrp1	MDCKII-OAT1/BCRP, Proximal Tubule Cell Monolayer
Absorption	MDR1, BCRP	rMdr1b, rBcrp1, rMrp2	Caco-2 Caco-2 KO
Blood-Brain Barrier	MDR1, BCRP, OATP2B1, OATP1A2, MRP4, MRP5	rMdr1a, rBcrp1,cyno OATPs, rat OATPs	RBEC, MBEC, MDCKII-MDR1

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Human Transporter Models

Regulatory

MDR1	ASBT	MRP4	OSTα/β
BCRP	CNT1	MRP5	PEPT1
BSEP	CNT2	NTCP	PEPT2
OATP1B1	CNT3	OAT2(v1)	SGLT1
OATP1B3	ENT1	OAT4	SGLT2
OAT1	ENT2	OATP1A2	SGLT5
OAT3	ENT4	OATP2A1	SGLT6
OCT1	HPT1	OATP2B1	URAT1
OCT2	MRP1	OCT3	
MATE1	MRP2	OCTN1	
MATE2-K	MRP3	OCTN2	

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Preclinical Animal Transporter Models

Mouse	Rat	Dog	Cyno
Bcrp	Bsep	Bsep	Mdr1
Bsep	Mdr1b	Sglt2	Bcrp
Mdr1a	Mrp2		Bsep
Sglt2	Mrp3		Ntcp
	Asbt		Oatp1b1
	Ntcp		Oatp1b3
	Oat1		Oatp2b1
	Oatp1a1		
	Oatp1a4		
	Oatp1b2		
	Octn2		
	Ostα/β		

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Key Considerations of study design

Physicochemical characteristics of Test Article

- End point (Radiolabel, LC/MS, fluorescence)
- Passive permeability (assay suitability)
- Non-specific binding (add serum protein?)
- Solubility (solvent tolerance of assay)
- Cytotoxicity (duration of assay, or alternative use of vesicles)

Experimental conditions

- Linear transport rate conditions
- Effect of preincubation with inhibitor
- Recovery of Test Article (mass balance)
- Substrate-dependent inhibition

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Assay selection

Available budget
Physicochemical properties of compound
Regulatory or mechanistic?
Barrier/Tissue of interest
Downstream application (ie. PBPK modeling)
Cross-species comparison

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Assays used to study transporters

Individual transporter models

- Vesicular transport
- Cell monolayer
- Cellular uptake

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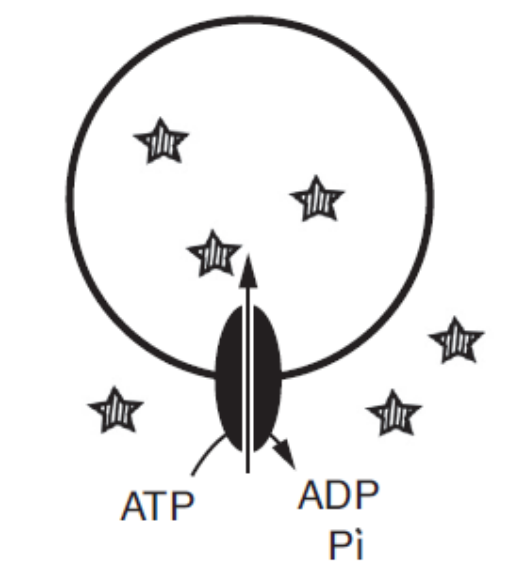
Vesicular Transport Assay

- ✓ Quick, simple, and high throughput
- ✓ Flexible readout (LSC, Fluor, LC/MS)
- ✓ Inhibition assays: works with high, medium, or low permeability compounds
- ✓ Mammalian membrane vesicles available, providing more physiologically relevant system
- ✓ All membrane vesicles required are generated in-house at SOLVO
- × Substrate assays: only for low permeability compounds



VT - Substrate assay

- Study accumulation using ATP vs. AMP in both transporter overexpressing and non-expressing vesicles in the absence and presence of specific reference inhibitor.
- Further enzyme kinetics can be studied (determination of K_m and V_{max}).

VT - Inhibition assay

- Study inhibition of a known probe substrate in vesicles overexpressing a selected transporter.
- Use two or seven concentrations of the compound which is tested as inhibitor.
- An IC_{50} value can be determined (at seven concentrations).
- Alternatively, determine the K_i value.

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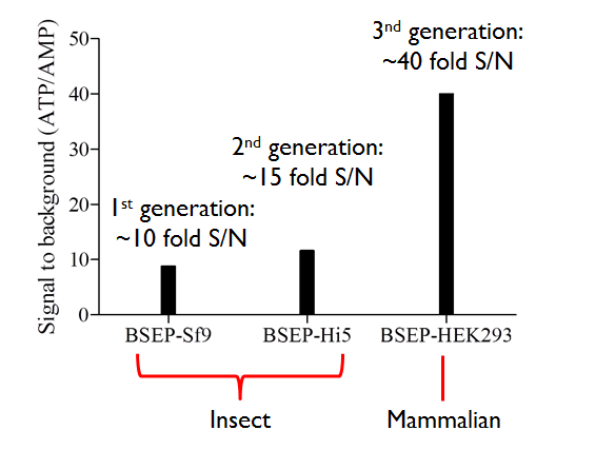
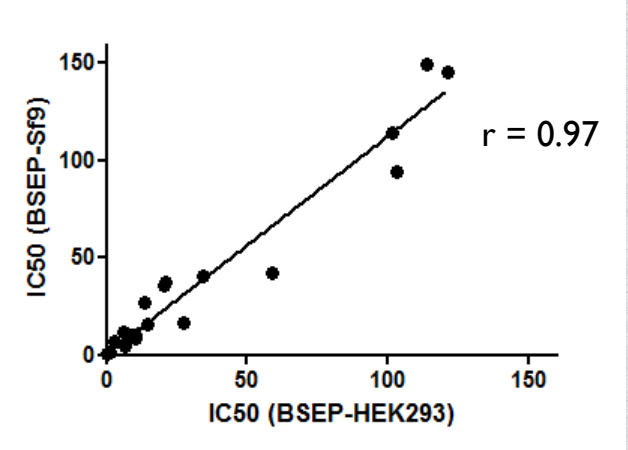
Why use HEK293 vesicles?



~40-fold dynamic range using BSEP-HEK293 vesicles, compared to ~10-fold using traditional Sf9 insect membranes.



Comparison study using 31 reference compounds show no difference in IC_{50} values using BSEP-Sf9 or BSEP-HEK293 vesicles.

IC_{50} values correlate well between BSEP-Sf9 and BSEP-HEK293, however HEK293 have a **superior activity** and assay performance.

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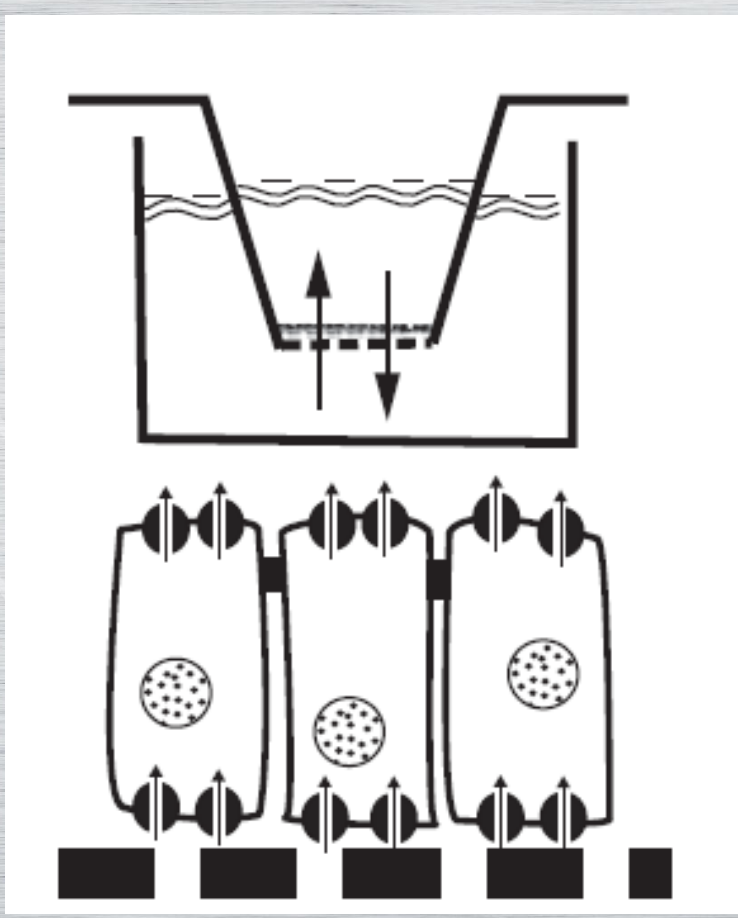
Bidirectional transport assay in polarized cells

Monolayer assay cells contain ATPaseBinding Casette (ABC) or efflux transporters, several formats available (MDCKII, LLC-PK1, or Caco-2), the cells form a tight barrier, separating two compartments (apical and basolateral).

- ✓ Permeation (or flux) of a compound across the cell monolayer can be measured.
- ✓ Gold standard for modeling permeability
- ✓ Addresses active transport Vs passive diffusion
- × May not be suitable for low permeability compounds
- × Cell culturing conditions can be challenging, leading to inter-lab variability



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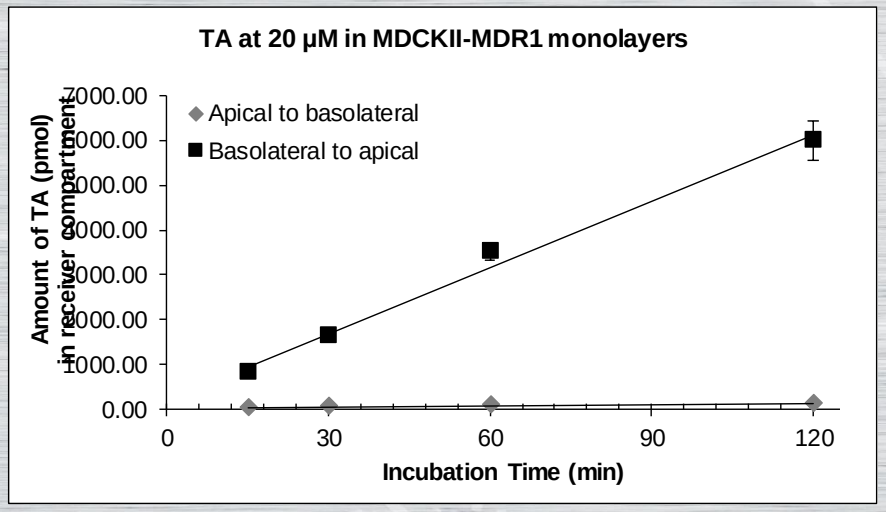
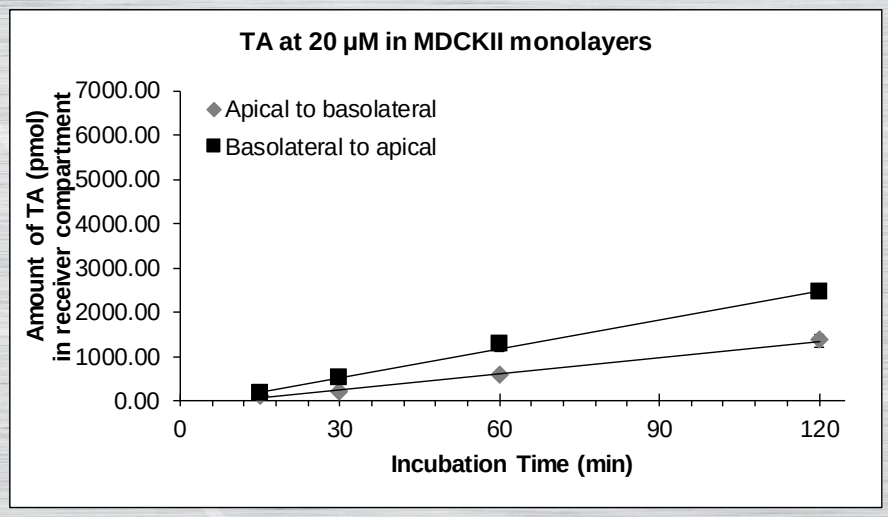
Monolayer assay – substrate testing





$P_{app,BA}$= 61
$P_{app,AB}$= 1.4
ER= 44, thus a substrate in the MDR1 expressing monolayer

$P_{app,BA}$= 24
$P_{app,AB}$= 13
ER= 1,8 thus minimal substrate activity of endogenous transporters.

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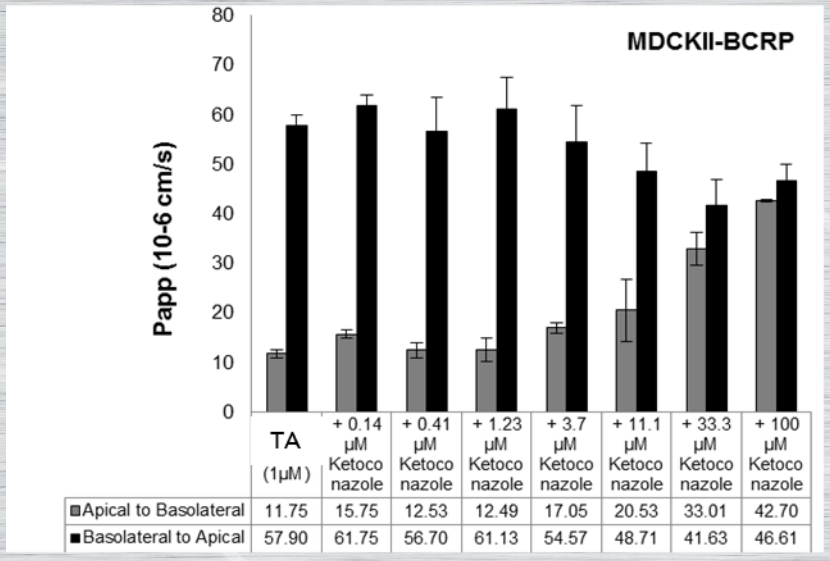
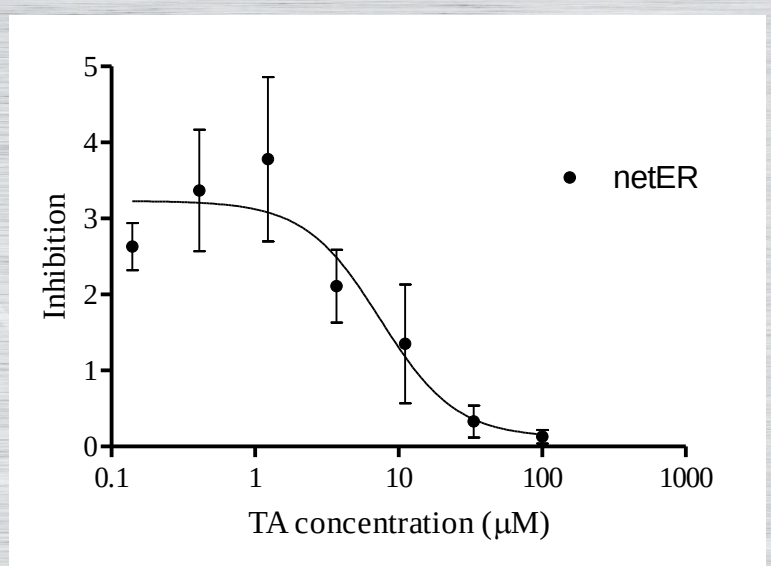
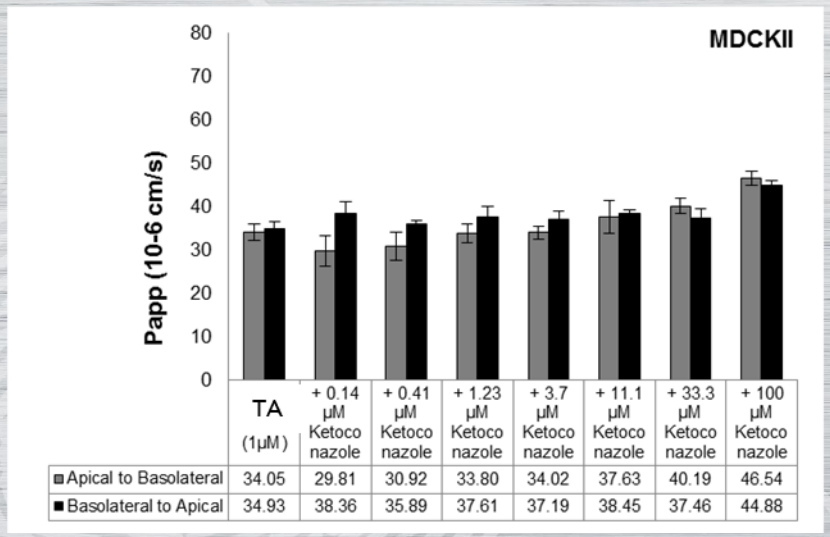
Monolayer assay – inhibition testing



	TA (1µM)	+ 0.14 µM Ketoconazole	+ 0.41 µM Ketoconazole	+ 1.23 µM Ketoconazole	+ 3.7 µM Ketoconazole	+ 11.1 µM Ketoconazole	+ 33.3 µM Ketoconazole	+ 100 µM Ketoconazole
Apical to Basolateral	11.75	15.75	12.53	12.49	17.05	20.53	33.01	42.70
Basolateral to Apical	57.90	61.75	56.70	61.13	54.57	48.71	41.63	46.61





	TA (1µM)	+ 0.14 µM Ketoconazole	+ 0.41 µM Ketoconazole	+ 1.23 µM Ketoconazole	+ 3.7 µM Ketoconazole	+ 11.1 µM Ketoconazole	+ 33.3 µM Ketoconazole	+ 100 µM Ketoconazole
Apical to Basolateral	34.05	29.81	30.92	33.80	34.02	37.63	40.19	46.54
Basolateral to Apical	34.93	38.36	35.89	37.61	37.19	38.45	37.46	44.88

- Inhibition of a probe substrate (prazosin) transport (by BCRP) = nER_i / nER_{max}

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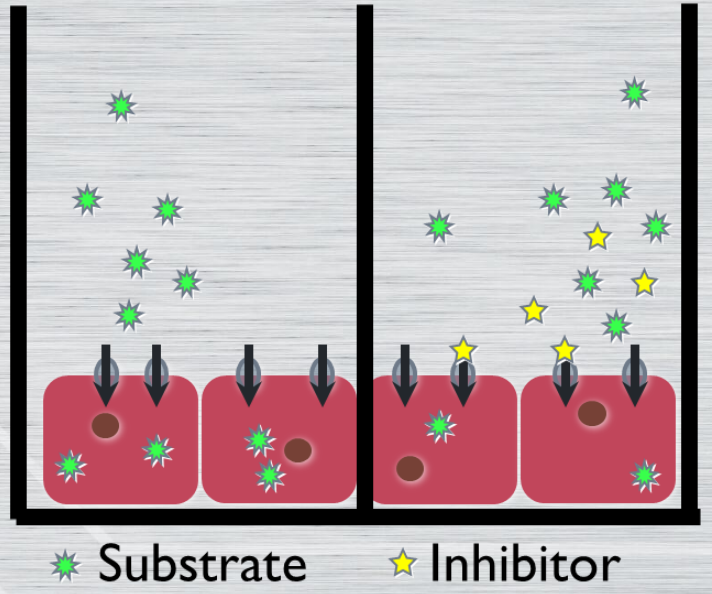
Cellular Uptake Assay

- ✓ Quick, simple, and high throughput
- ✓ Flexible readout (LSC, Fluor, LC/MS)
- ✓ Inhibition assays: works with high, medium, or low permeability compounds
- ✓ Many cell backgrounds available
- ✓ Stable cell lines are generated in-house at SOLVO
- × Substrate assays: high permeability compounds may be challenging



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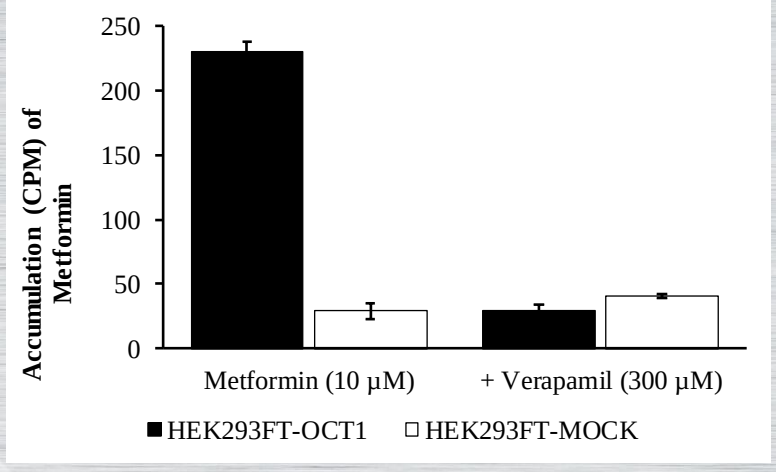
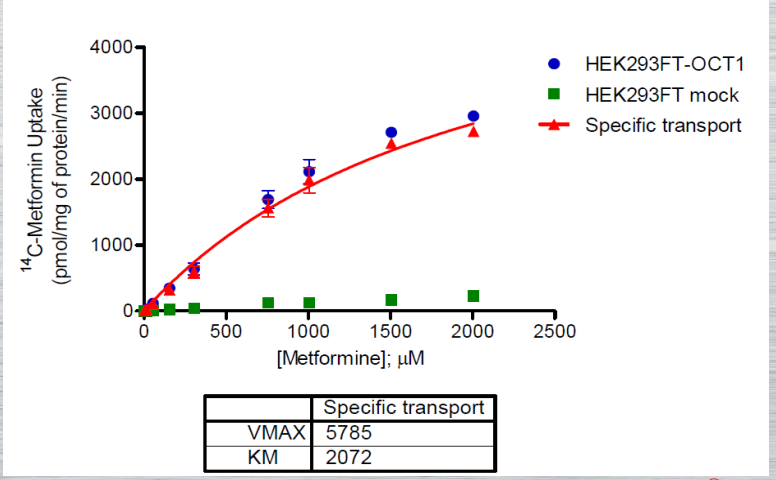
Uptake substrate assay

- Study accumulation in transporter expressing and non-transporter expressing cells (mock or parental) in the presence and absence of a specific reference inhibitor
- Further enzyme kinetics can be studied (determination of K_m and V_{max}).





	Specific transport
VMAX	5785
KM	2072

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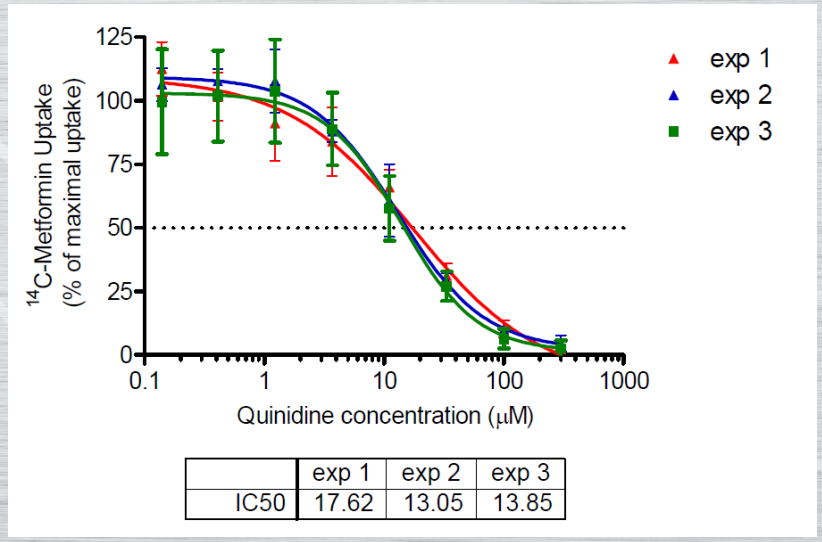
Uptake inhibition assay

- Study inhibition of a known probe substrate in transporter overexpressing and mock/parental cells.
- Use two or seven concentrations of the compound which is tested as inhibitor.
- An IC_{50} value can be determined (at seven concentrations).
- Alternatively, determine the K_i value.



	exp 1	exp 2	exp 3
IC50	17.62	13.05	13.85

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Assays used to study transporters

Holistic barrier models

- Proximal tubule cells
- Hepatocytes

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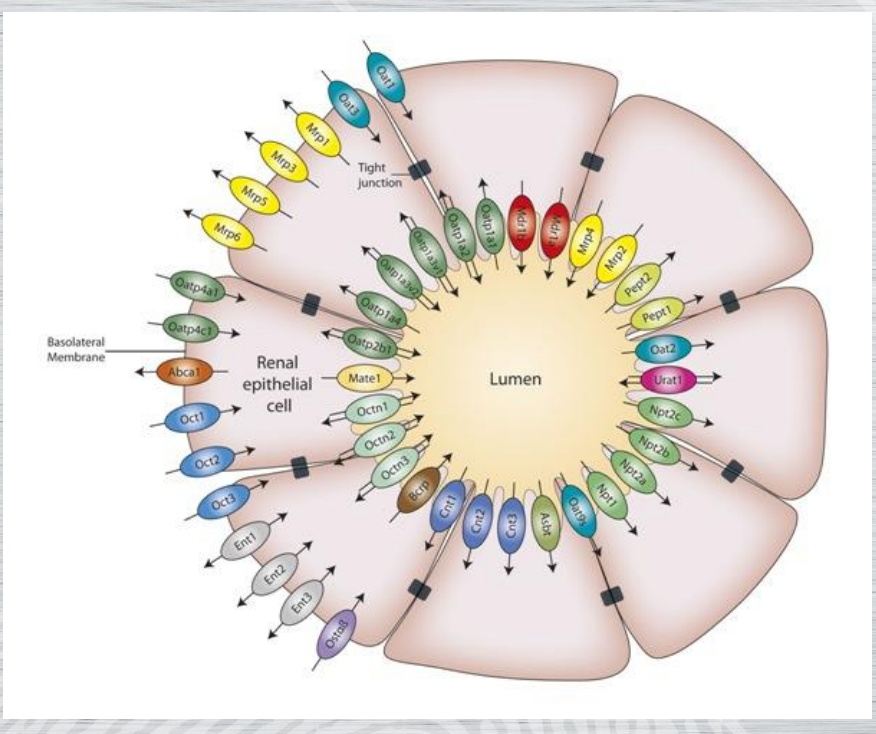
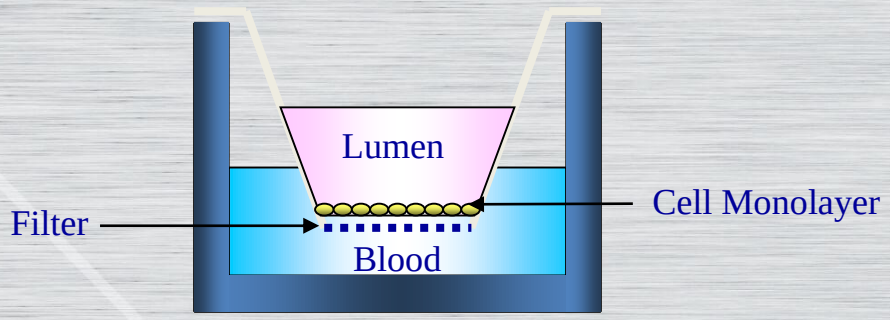
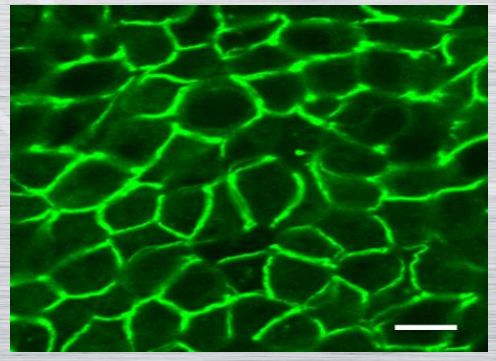
aProximate Proximal Tubule Cell Model

Proximal tubule cells isolated and plated <18 hours *ex vivo*







ZO-1 Expression

Offered in partnership with

Newcells BIOTECH

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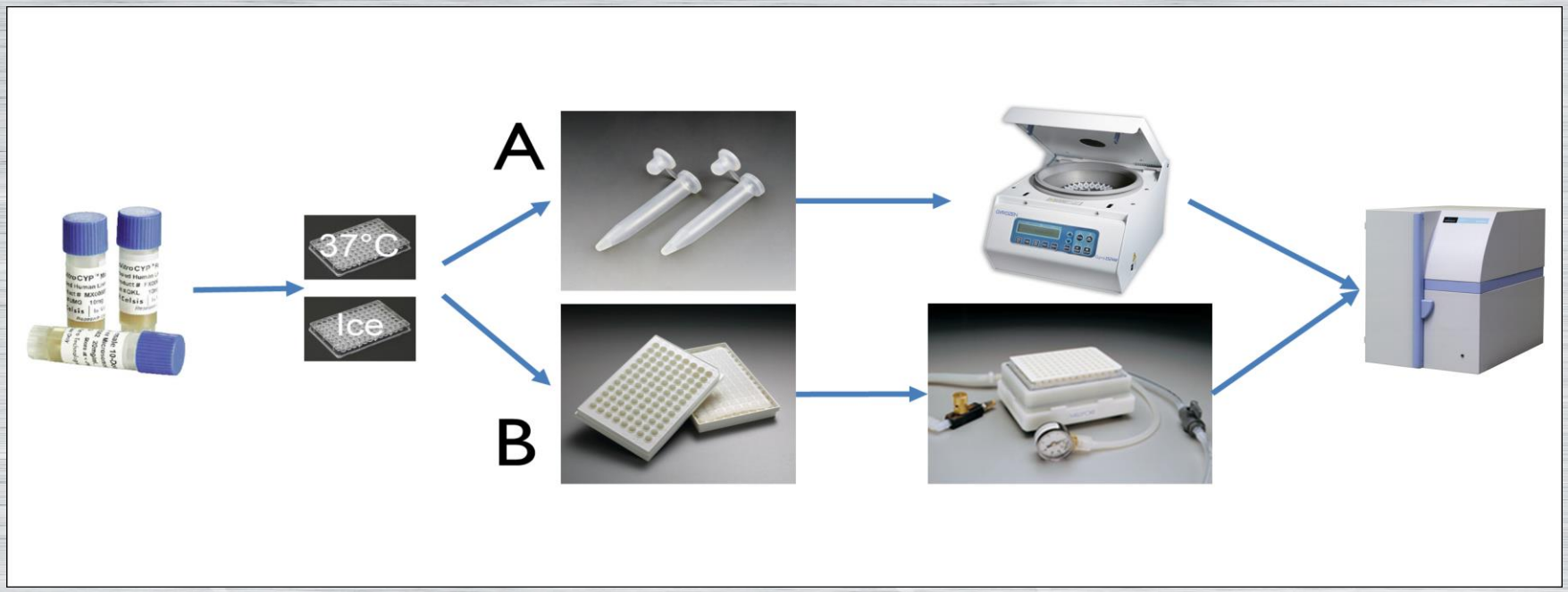
Suspension hepatocyte uptake assay



- ✓ Quick and easy assay
- ✓ Hepatocytes can be cryopreserved
- ✓ Good tools for identifying substrate of hepatic uptake transporters
- ✓ Assess the contribution of passive vs active processes

- × Individual transporter can not be determined
- × Not suitable for measuring canalicular efflux
- × Differences between donors (pooled donors)

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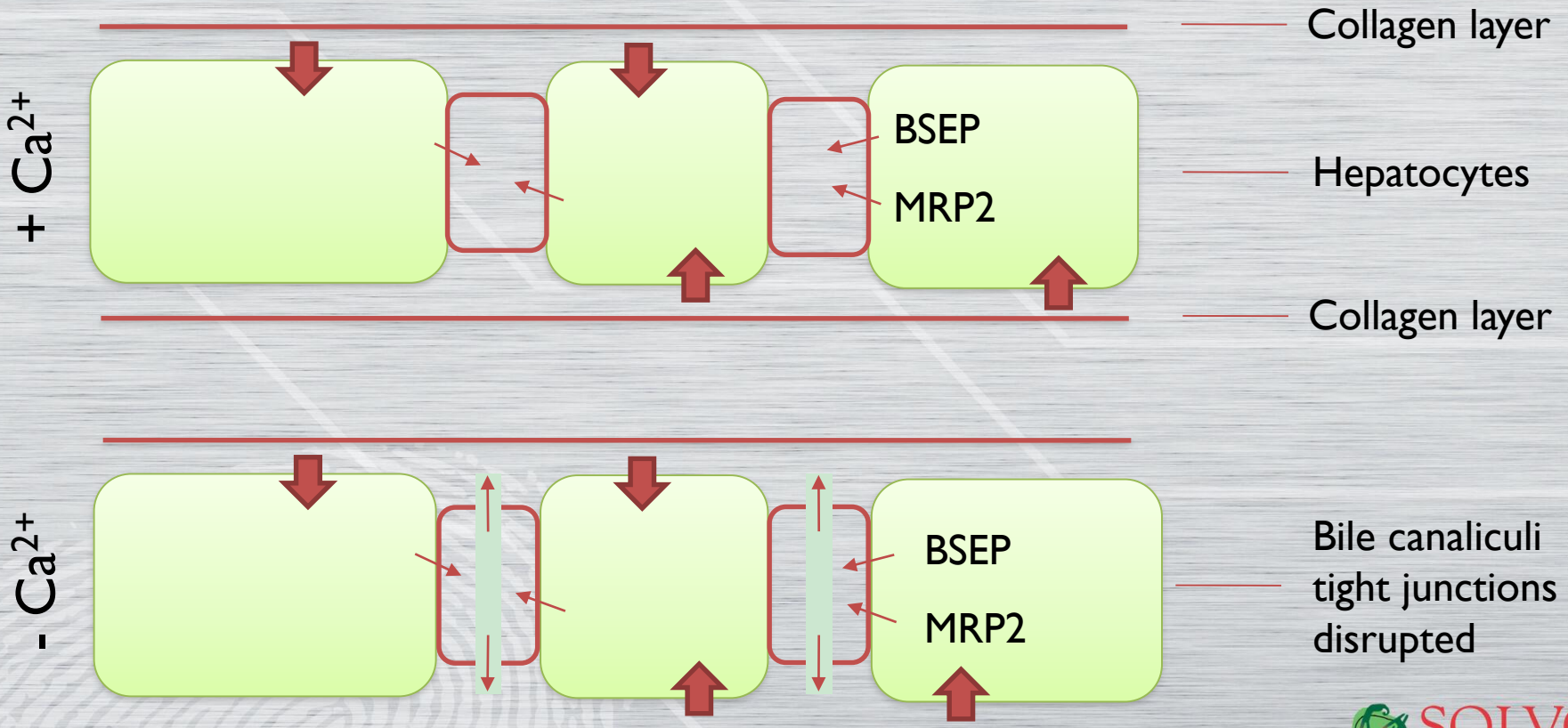
Sandwich cultured hepatocytes

B-Clear® Technology

- Determine Biliary Efflux Rate by measuring in the presence and absence of Ca^{2+}
- Measure hepatic uptake



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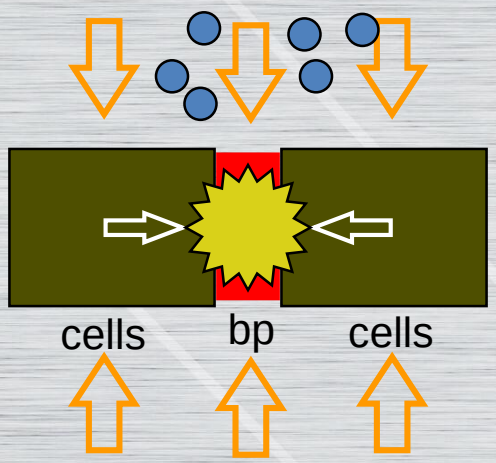
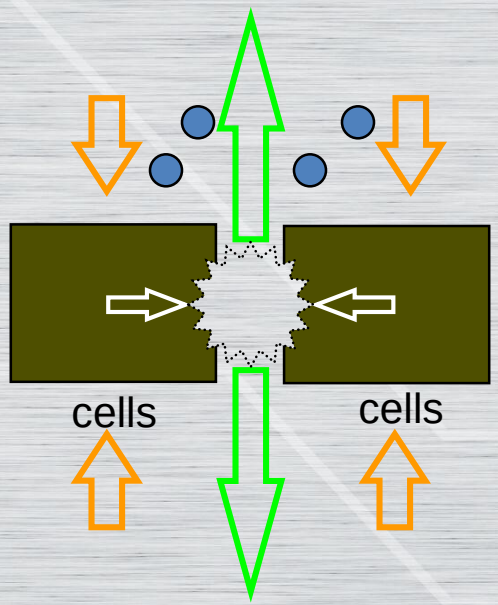
Plus (+) Buffer (junctions tight)



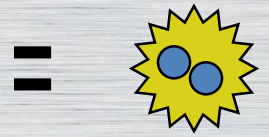
*Measures compound inside hepatocytes **AND** in bile pockets, i.e. total taken up*

Minus (-) Buffer (junctions open)



*Measures compound only inside hepatocytes, i.e. amount taken up but **NOT** excreted*

Difference



Subtraction – determine amount of compound excreted in bile

Courtesy from Qualyst Transporter Solutions, Inc.

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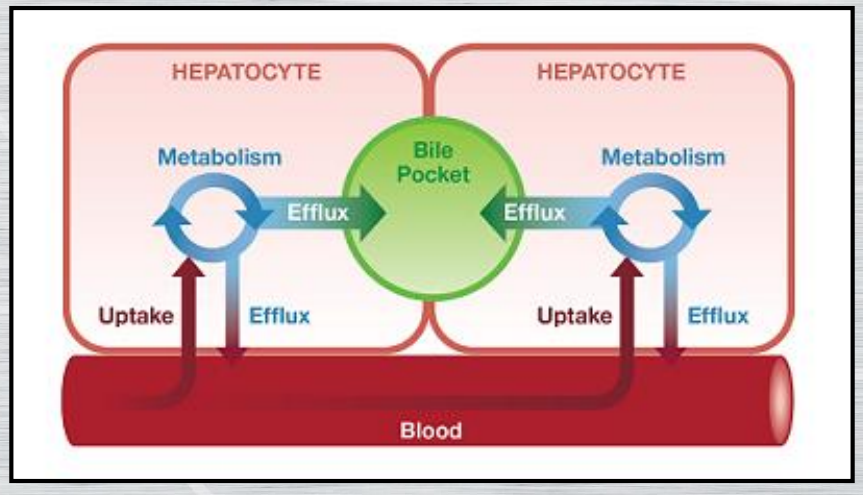
Sandwich cultured hepatocytes

B-Clear® Technology

- ✓ Can measure uptake and efflux (basolateral and canalicular)
- ✓ Cross-species comparison
- ✓ Transporter-metabolism interplay
- ✗ Relatively expensive, low throughput assay
- ✗ Difficult to measure low clearance compounds



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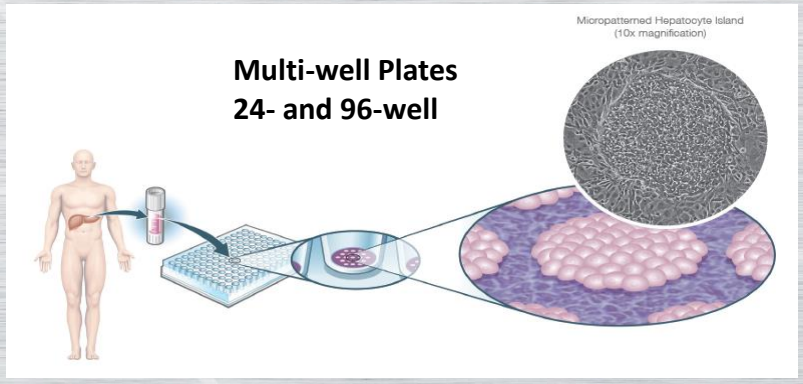
In vitro liver models

Suspension Hepatocytes → Sandwich Cultured Hepatocytes → **Micropatterned Hepatocytes**

Complexity, functionality, longelivity

- HepatoPac® Micro-patterned Co-Cultures (MPCCs)
- Engineered to Deliver *In Vivo* Like Hepatic Performance
- Morphology and metabolic function remain steady for 28 days or longer



Khetani and Bhatia. Nature Biotech 26(1) 2008

Courtesy from Ascendance Biotechnology, Inc.

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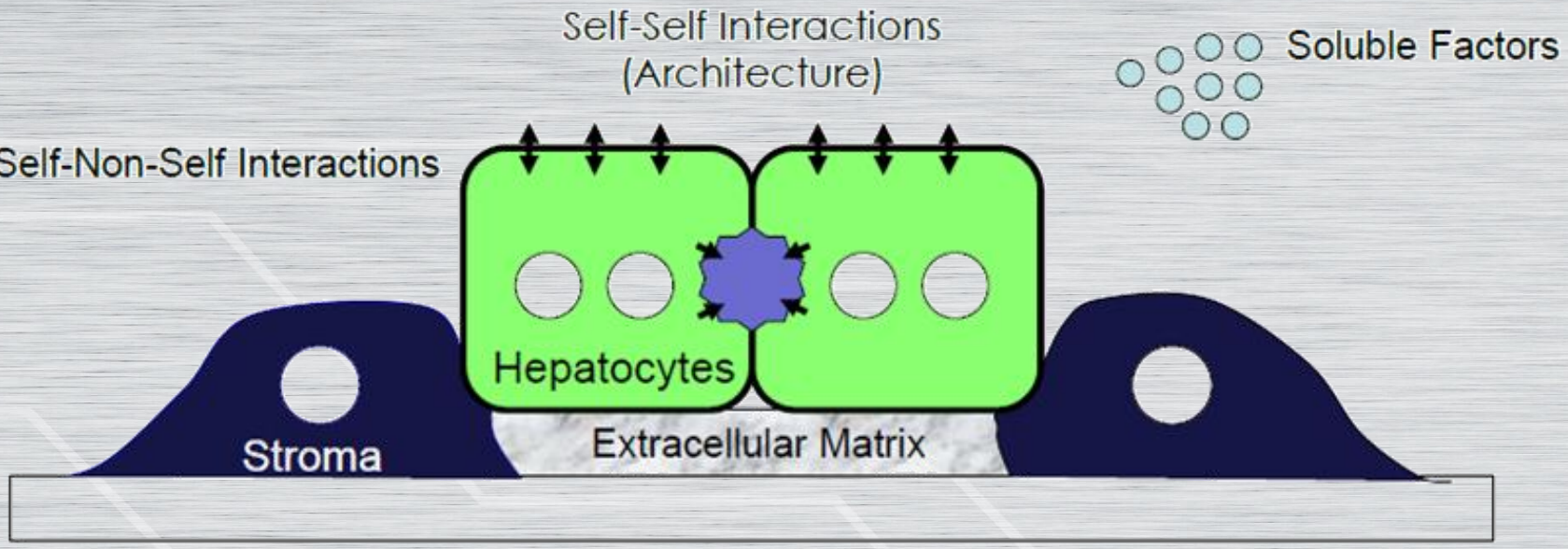
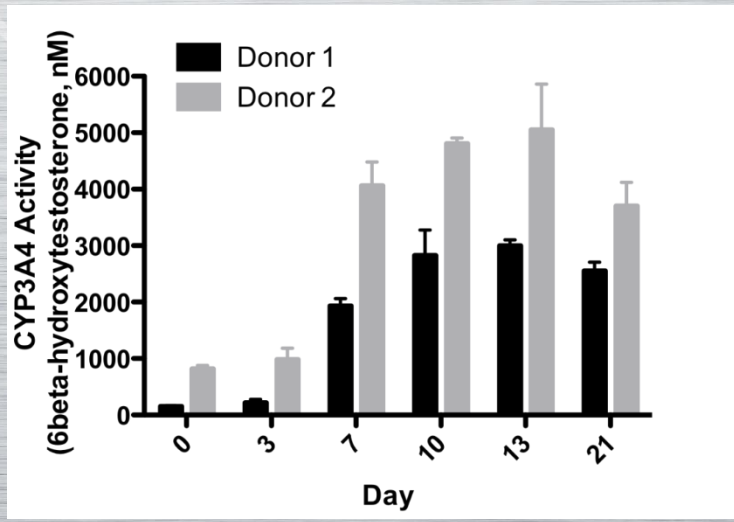
Micropatterned co-cultures (HepatoPac™)



Complex architecture of system leads to:

- Improved viability of cells
- Improved functionality of cells
- Robustness and reproducibility of the system



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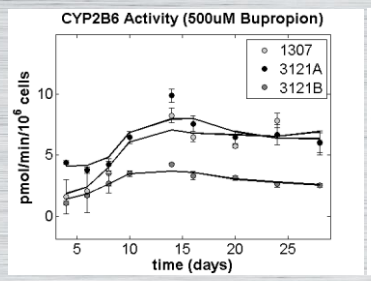
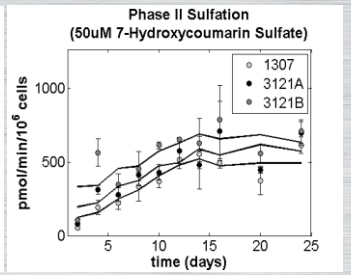
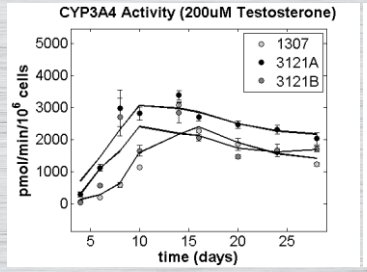
HepatoPac

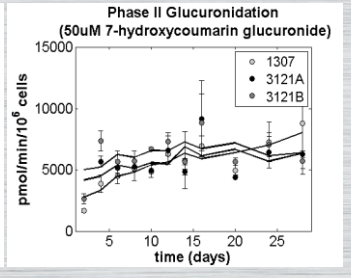
Complex *in vitro* systems such as HepatoPac (micropatterned hepatocytes):

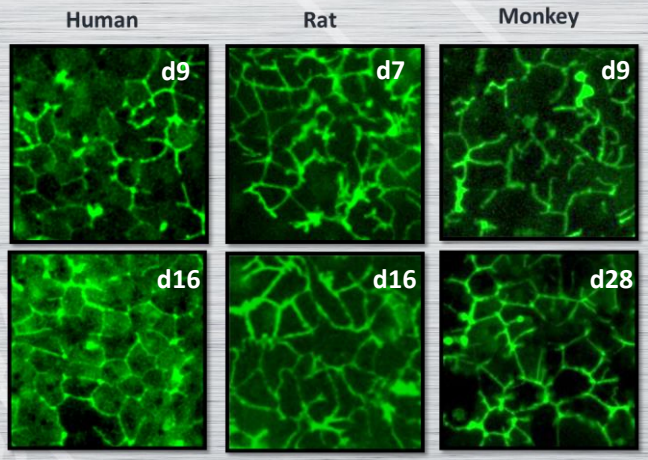
- Express apical and basolateral transporters
- Have functional bile-pockets
- Show CYP450 and phase II metabolic activity
- Possess longevity of up to 4 weeks.
- Main uses for:
  - Low turnover clearance (metabolism)
  - MetID
  - Toxicity testing











Fluorescent MRP2 probe substrate CDCF accumulates in bile pockets of human, rat and monkey hepatocytes for up to 28 days in culture.

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Micropatterned co-cultures (HepatoPac™) - Applications

- ✓ Metabolite ID
- ✓ Clearance studies (esp. low clearance compounds)
- ✓ Cross-species comparison
- ✓ Toxicity (esp. long-term incubation)
- ✓ Inflammation (with Kupffer cells – HepatoMune™)
- × Expensive assay system
- × Limited hepatocyte number/plate can make transport experiments challenging

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Metabolism

- Under development at SOLVO:
  - Metabolic stability (Microsomes, S9)
  - CYP inhibition (Microsome, Bactosomes)
  - CYP induction (Hepatocytes)
- Allows running CYP and Transporter studies under one roof.

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SOLVO Advantage

- Deep understanding of transporters
  - 20 years of experience
  - First company to commercialize transporter assays
  - Dedicated R&D team, over 85 transporter publications
  - Flexibility in experimental set-up, from initial screening, through regulatory study design, to detailed kinetic characterization

- In-house reagent generation and assay development
  - Not dependent on external reagent suppliers
  - Thorough understanding of assays and experimental variables
  - Experience with custom assay development in multiple assay formats
  - Widest range of transporter products and services on market

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Science letters

UPTAKE TRANSPORTER PREINCUBATION -

why it is important and how it works

INTRODUCTION

Inhibition of a hepatic or renal uptake transporter by a drug (the "perpetrator") may profoundly alter the pharmacokinetics (PK) of co-administered drugs (the "victims") that depend on the affected transporter for target access and/or clearance. The classic example of transporter-mediated drug-drug interactions (DDIs) is the interference of cyclosporin A with the OATP-mediated uptake of statins into hepatocytes (Hirano et al., 2006). By inhibiting the active cellular uptake of statins, cyclosporin A restrains their access to their hepatic target and increases exposure of peripheral tissues; thus, it simultaneously limits the efficacy of statins and increases the potential for adverse effects [1].

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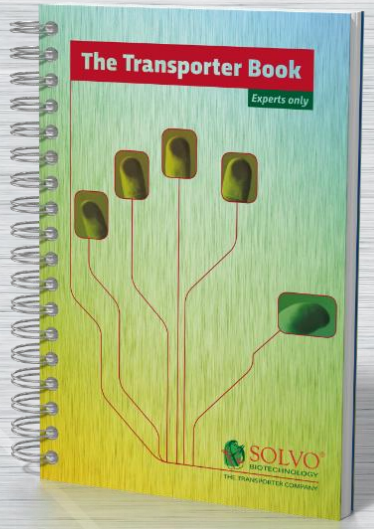
Transporter Book



- Why are transporters important?
- What are the expectations of regulatory agencies?
- How to study transporters?
- When should transporters be studied?
- Which transporters to study?

http://www.solvobiotech.com/knowledge-center/transporter-book-login

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SOLVO Webinars

Leveraging relationships with key opinion leaders, including:

- Caroline Lee
- Jash Unadkat
- Les Benet
- Gerry Kenna
- Maciej Zamek-Gliszczynski
- David Rodrigues
- Dhiren Thakker
- Oliver Langer
- Colin Brown
- Salman Khetani
- Birk Poller
- Mary Paine
- Ken Brouwer

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Thank you for your attention!

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