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# Transporters and Drug-Drug Interactions: Important Determinants of Drug Disposition and Effects<sup>§</sup>

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**Abstract**—Uptake and efflux transporters determine plasma and tissue concentrations of a broad variety of drugs. They are localized in organs such as small intestine, liver, and kidney, which are critical for drug absorption and elimination. Moreover, they can be found in important blood-tissue barriers such as the blood-brain barrier. Inhibition or induction of drug transporters by coadministered drugs can alter pharmacokinetics and pharmacodynamics of the victim drugs. This review will summarize in particular clinically observed

drug-drug interactions attributable to inhibition or induction of intestinal export transporters [P-glycoprotein (P-gp), breast cancer resistance protein (BCRP)], to inhibition of hepatic uptake transporters [organic anion transporting polypeptides (OATPs)], or to inhibition of transporter-mediated [organic anion transporters (OATs), organic cation transporter 2 (OCT2), multidrug and toxin extrusion proteins (MATEs), P-gp] renal secretion of xenobiotics. Available data on the impact of nutrition on transport processes as well as

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genotype-dependent, transporter-mediated drug-drug interactions will be discussed. We will also present and discuss data on the variable extent to which information on the impact of transporters on drug disposition is included in summaries of product characteristics of

selected countries (SPCs). Further work is required regarding a better understanding of the role of the drug metabolism–drug transport interplay for drug-drug interactions and on the extrapolation of in vitro findings to the in vivo (human) situation.

## I. Introduction

Drug transporters are now well recognized determinants of drug disposition and effects (Giacomini et al., 2010; Klaassen and Aleksunes, 2010; Zolk and Fromm, 2011). Functionally, they can be classified into transporters mediating the uptake of drugs into cells and transporters mediating the export of drugs or drug metabolites out of cells. Each transporter has a specific pattern of tissue expression. Transporters expressed in the small intestine, the liver, and the kidney are of particular importance for drug disposition and drug-drug interactions (Shitara et al., 2005; Müller and Fromm, 2011; Zhang et al., 2011; Lepist and Ray, 2012; Morrissey et al., 2013; Yoshida et al., 2013). Moreover, transporters expressed in blood-tissue barriers, such as the blood-brain barrier or the maternal-fetal barrier, have been shown to protect sensitive tissues from potentially toxic compounds.

Efflux transporters such as P-glycoprotein (P-gp; gene symbol *ABCB1*; Table 1), the breast cancer resistance protein (BCRP; gene symbol *ABCG2*), and the multidrug resistance protein 2 (MRP2; gene symbol *ABCC2*) are localized to the apical membrane of enterocytes (Fig. 1), thereby limiting bioavailability of orally administered substrates. Inhibition of these efflux transporters by concomitantly administered drugs results in an increased bioavailability of the victim drug, whereas induction of these intestinal efflux transporters reduces bioavailability of drug substrates. After absorption and passage through the portal vein, drugs reach the basolateral membrane of hepatocytes (Fig. 2). Here, expression of uptake transporters for organic anions (e.g., organic anion-transporting polypeptides such as OATP1B1, gene symbol *SLCO1B1*; Table 1) and organic cations (e.g., organic cation transporters such as OCT1, gene symbol *SLC22A1*) mediate uptake of the substrates (e.g., statins) into hepatocytes, the most important site of drug metabolism. Efflux transporters localized in the canalicular membrane of hepatocytes [(e.g., P-gp, BCRP, multidrug and toxin extrusion protein 1 (MATE1, gene symbol *SLC47A1*), multidrug resistance protein 2 (MRP2), bile salt export pump (BSEP, gene symbol *ABCB11*)] mediate transport of drugs, phase I or phase II drug metabolites, and endogenous compounds into bile. Drug transporters also play a major role for drug

secretion from the proximal tubular cells of the kidney into urine (Fig. 3). Secretion of cationic drugs is mediated by uptake via OCT2 (gene symbol *SLC22A2*) localized in the basolateral membrane and subsequent efflux by MATE1 and MATE2-K (gene symbol *SLC47A2*) localized in the luminal membrane of proximal tubular cells. Similarly, uptake and efflux transporters for organic anions are also expressed in the kidney. Inhibition of these processes by concomitantly administered drugs leads to a reduced renal clearance of the victim drug.

This review intends to summarize the current knowledge on transporter-mediated drug-drug interactions combining data from in vitro studies (Table 2) with drug interaction studies in humans (Table 3). The impact of food constituents on transporter-mediated drug elimination and the impact of drugs on elimination of endogenous substances will also be addressed.

## II. Expression and General Function of Uptake and Efflux Transporters

This section summarizes data regarding molecular features, tissue expression, and substrate specificity of drug transporters discussed in this review. If not stated otherwise, all data regarding the substrate specificity of a transporter presented in section II are based on studies using in vitro cell models (e.g., transfected cell lines or oocytes overexpressing the respective human transporter). The clinical relevance of these in vitro data is discussed in section III. Other models for investigating substrate spectra of human transport proteins or the role of a given human transporter for the disposition of endogenous compounds or drugs are humanized mouse lines that have been established for several human transport proteins (Scheer et al., 2012; van de Steeg et al., 2012, 2013; Zimmermann et al., 2013).

Because of the mode of action, transport proteins can be grouped into uptake transporters mediating the transport of substances from outside into cells and export proteins transporting substances out of cells. Whereas all uptake transporters belong to the superfamily of SLC (solute carriers) transporters, most export proteins are members of the ABC transporter (ATP-binding cassette) superfamily with the exception of the MATE (multidrug and toxin extrusion) proteins, which are also members of the SLC transporter superfamily.

**ABBREVIATIONS:** AUC, area under the plasma/serum concentration-time curve; BSEP, bile salt export pump; BCRP, breast cancer resistance protein;  $C_{max}$ , maximal plasma/serum concentration; CNS, central nervous system; CsA, cyclosporine; EMA, European Medicines Agency; FDA, Food and Drug Administration; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; MATE, multidrug and toxin extrusion protein; MRP2, multidrug resistance protein 2; NMN, *N*-methylnicotinamide; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; OCT, organic cation transporter; P-gp, P-glycoprotein; SLC, solute carrier; SPCs, summaries of product characteristics.

TABLE 1  
Characteristics of selected drug transporters

Protein	Amino Acids	Direction	Family	Gene	Chromosome	Accession Number
P-gp	1280	Export	<i>ABCB</i>	<i>ABCB1</i>	7q21.12	NM_000927
BSEP	1321	Export	<i>ABCB</i>	<i>ABCB11</i>	2q24	NM_003742
MRP2	1545	Export	<i>ABCC</i>	<i>ABCC2</i>	10q24	NM_000392
BCRP	655	Export	<i>ABCG</i>	<i>ABCG2</i>	4q22	NM_004827
MATE1	570	Export	<i>SLC47</i>	<i>SLC47A1</i>	17p11.2	NM_018242
MATE2-K	602	Export	<i>SLC47</i>	<i>SLC47A2</i>	17p11.2	NM_152908
OATP1A2	670	Uptake	<i>SLC21/SLCO</i>	<i>SLCO1A2</i>	12p12	NM_134431
OATP1B1	691	Uptake	<i>SLC21/SLCO</i>	<i>SLCO1B1</i>	12p12	NM_006446
OATP1B3	702	Uptake	<i>SLC21/SLCO</i>	<i>SLCO1B3</i>	12p12	NM_019844
OATP2B1	709	Uptake	<i>SLC21/SLCO</i>	<i>SLCO2B1</i>	11q13	NM_007256
OCT1	554	Uptake	<i>SLC22</i>	<i>SLC22A1</i>	6q25.3	NM_003057
OCT2	555	Uptake	<i>SLC22</i>	<i>SLC22A2</i>	6q25.3	NM_003058
OCT3	556	Uptake	<i>SLC22</i>	<i>SLC22A3</i>	6q25.3	NM_021977
OAT1	563	Uptake	<i>SLC22</i>	<i>SLC22A6</i>	11q12.3	NM_004790
OAT2	546	Uptake	<i>SLC22</i>	<i>SLC22A7</i>	6p21.1	NM_006672
OAT3	542	Uptake	<i>SLC22</i>	<i>SLC22A8</i>	11q11	NM_004254
OAT4	550	Uptake/efflux	<i>SLC22</i>	<i>SLC22A11</i>	11q13.1	NM_018484

General molecular properties of uptake transporters and export pumps such as protein length, chromosomal localization, or the accession number of the reference cDNA sequence encoding the respective transporter are summarized in Table 1.

#### A. Uptake Transporters

1. *The OATP Family (SLC Family SLC21/SLCO).* The human OATP family (gene symbol *SLC21/SLCO*) consists of 11 members grouped into six subfamilies [OATP1–OATP6 (Hagenbuch and Meier, 2004)] based on their amino acid sequence similarities. From these OATP proteins, to this day four have been identified as being important for drug therapy (Figs. 1–4). In detail, these are the family members: OATP1A2 (gene symbol *SLCO1A2*), reported to be expressed in the intestinal epithelium (Glaeser et al., 2007), the renal epithelium, and highly expressed in brain capillary endothelial cells [Fig. 4 (Gao et al., 2000; Lee et al., 2005)]; the

closely related OATPs OATP1B1 [Supplemental Fig. 1 (gene symbol *SLCO1B1*)] and OATP1B3 (gene symbol *SLCO1B3*), both highly if not exclusively expressed in human hepatocytes [Fig. 2 (Abe et al., 1999; Hsiang et al., 1999; König et al., 2000a,b)]; and OATP2B1 (gene symbol *SLCO2B1*), the OATP family member being expressed in almost all tissues investigated thus far (Kullak-Ublick et al., 2001; Kobayashi et al., 2003; Grube et al., 2006). It is noteworthy that, in addition to the expression in normal tissues, some studies demonstrated the upregulation of OATP proteins in several malignant tissues. Altered OATP1A2 expression for example has been demonstrated in gliomas (Bronger et al., 2005), whereas OATP1B3 seems to be expressed in colon polyps, colon cancer (Lee et al., 2008; Lockhart et al., 2008), and in pancreatic adenocarcinoma (Hays et al., 2013). A detailed analysis of the quantitative and

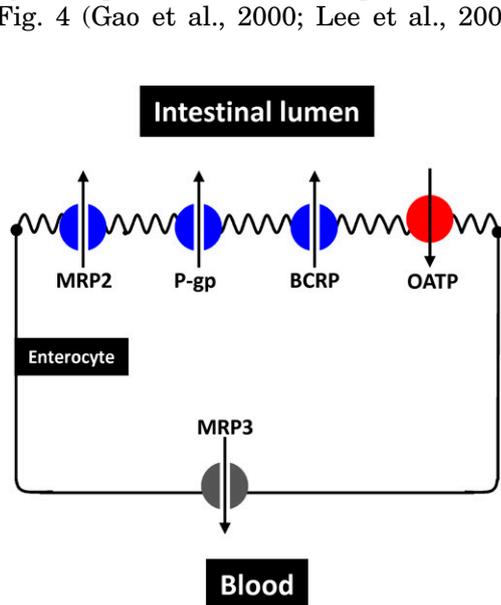


Fig. 1. Transporters expressed in enterocytes of the human intestinal epithelium. Uptake transporters discussed in this review are colored in red, export pumps in blue.

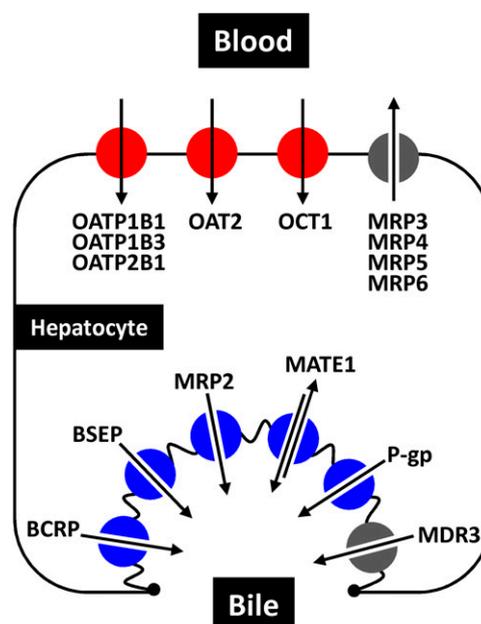
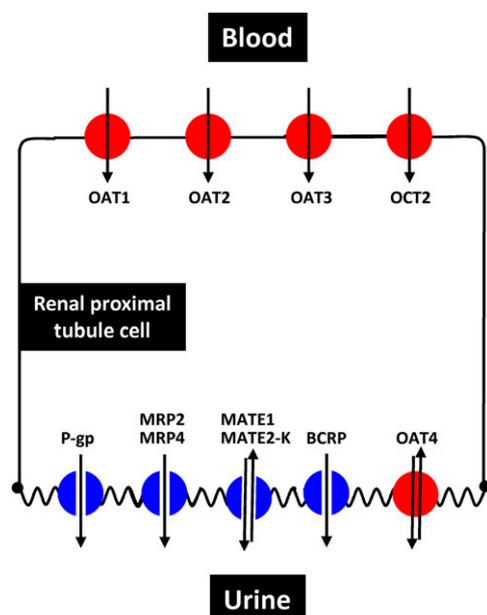


Fig. 2. Transporters expressed in human hepatocytes. Uptake transporters discussed in this review are colored in red, export proteins in blue.



**Fig. 3.** Transporters expressed in human renal proximal tubule epithelial cells. Uptake transporters discussed in this review are colored in red, export proteins in blue.

markedly variable expression of OATP1B1, OATP1B3, and OATP2B1 mRNA and protein in human livers and of factors contributing to this variability has been published recently (Nies et al., 2013).

In vitro data indicate that OATPs share an overlapping but not identical substrate spectrum and transport a variety of amphipathic substances, including

several endogenously synthesized metabolites such as bile acids, thyroid hormones, or hormone conjugates (Meyer zu Schwabedissen et al., 2011). Furthermore, several widely prescribed drugs have been identified as substrates for OATPs, and therefore, these play an important role for drug disposition (for an overview of OATP substrates see the following reviews: König et al., 2006; Fahrmayr et al., 2010; König, 2011; Niemi et al., 2011). An important drug class with compounds being transported by OATP1A2, OATP1B1, OATP1B3, and OATP2B1 are HMG-CoA reductase inhibitors (statins). Pitavastatin has been identified as substrate for all four OATPs (Shirasaka et al., 2011), whereas other statins such as pravastatin are transported by OATP1B1 (Hsiang et al., 1999) and OATP1B3 (Seithel et al., 2007). In addition, several other drugs have been identified as substrates for these OATP family members, including antibiotics, chemotherapeutic agents, antihistaminic drugs, and diuretics (Table 2). Humanized OATP1B1 and OATP1B3 transgenic mice are now available and have contributed to a better understanding of the role of those transporters for the disposition of conjugated bilirubin, methotrexate, paclitaxel, and sorafenib (van de Steeg et al., 2012, 2013; Zimmermann et al., 2013).

2. *The OAT/OCT Family (SLC Family SLC22)*. The SLC22 family of organic cation/anion/zwitterion transporters consists of 23 human members, including the cation transporters OCTs, the anion transporters OATs (Supplemental Fig. 1), the organic cation/carnitine transporters OCTNs, and several other related

TABLE 2  
Transporter substrates and corresponding in vitro/in vivo inhibitors (examples with availability of  $IC_{50}/K_i$  values)

Transporter	Selected Substrates	Selected Inhibitors	$IC_{50}$ or $K_i^a$	Reference
			$\mu M$	
OATP1A2	Aliskiren	Naringin	75.5	Rebello et al., 2012
	Fexofenadine	Apigenin	9.3	Mandery et al., 2010
	Fexofenadine	Hesperidin	2.7	Bailey, 2010
	Fexofenadine	Naringin	3.6–24.2	Bailey, 2010; Rebello et al., 2012
OATP2B1	Fexofenadine	Apigenin	13.9	Mandery et al., 2010
	Rosuvastatin	Cyclosporine	0.07	Ho et al., 2006
	Rosuvastatin	Gemfibrozil	8	Ho et al., 2006
OATP1B1	Cerivastatin	Gemfibrozil	72	Shitara et al., 2004
		Gemfibrozil-1-O- $\beta$ -glucuronide	24	
	Pitavastatin	Cyclosporine	0.24 <sup>a</sup>	Hirano et al., 2006
	Pitavastatin	Clarithromycin	8.26 <sup>a</sup>	Hirano et al., 2006
	Rosuvastatin	Gemfibrozil	25	Ho et al., 2006
OATP1B3	Rosuvastatin	Cyclosporine	0.31	Ho et al., 2006
	Pravastatin	Erythromycin	40% Inhibition by 10 $\mu M$	Seithel et al., 2007
	Rosuvastatin	Cyclosporine	0.06	Ho et al., 2006
NTCP	Rosuvastatin	Cyclosporine	0.37	Ho et al., 2006
	Rosuvastatin	Gemfibrozil	23	Ho et al., 2006
OAT3	Methotrexate	Indomethacin	0.61–0.98	Burckhardt and Burckhardt, 2011
	Fexofenadine	Probenecid	1.3 <sup>a</sup>	Tahara et al., 2005
OCT1	Metformin	Cimetidine	104 <sup>a</sup>	Ito et al., 2012b
OCT2	Metformin	Cimetidine	124 <sup>a</sup>	Ito et al., 2012b
MATE1	Metformin	Cimetidine	3.8 <sup>a</sup>	Ito et al., 2012b
MATE2-K	Metformin	Cimetidine	6.9 <sup>a</sup>	Ito et al., 2012b
P-gp	Digoxin	Clarithromycin	4.1	Eberl et al., 2007
	Digoxin	Cyclosporine	1.3	Wandel et al., 1999
	Digoxin	Quinidine	2.2	Wandel et al., 1999
	Digoxin	Telithromycin	1.8	Eberl et al., 2007
	Digoxin	Verapamil	2.1	Wandel et al., 1999

<sup>a</sup>  $K_i$  value.

TABLE 3  
Clinically observed drug-drug interactions (selection) with involvement of drug transporters

Transporter(s)	Inhibitor	Victim	Pharmacokinetic Changes of Victim Drug	Reference
Intestinal OATPs	Grapefruit juice	Fexofenadine	p.o. ↓ AUC, $C_{max}$	Dresser et al., 2002; Glaeser et al., 2007
	Grapefruit juice	Celiprolol	p.o. ↓ AUC, $C_{max}$	Lilja et al., 2003
	Orange juice	Aliskiren	p.o. ↓ AUC, $C_{max}$	Tapaninen et al., 2011
Hepatic OATPs	Cyclosporine	Pravastatin	p.o. ↑ AUC, $C_{max}$	Olbricht et al., 1997; Park et al., 2002; Hedman et al., 2004
	Cyclosporine	Rosuvastatin	p.o. ↑ AUC, $C_{max}$	Simonson et al., 2004
Renal OATs	Gemfibrozil	Pravastatin	p.o. ↑ AUC, $C_{max}$ ; ↓ $Cl_r$	Kyrklund et al., 2003
	Probenecid	Furosemide	i.v. ↑ AUC, $C_{max}$ , $t_{max}$ ; ↓ $Cl_r$	Smith et al., 1980; Vree et al., 1995
			p.o. ↑ AUC; ↓ $Cl_r$	
Renal cation transporters (OCT2, MATEs)	Probenecid	Methotrexate	i.v. ↑ $C_{serum}$	Aherne et al., 1978
	Cimetidine	Metformin	p.o. ↑ AUC, $C_{max}$ ; ↓ $Cl_r$	Somogyi et al., 1987
	Cimetidine	Ranitidine	p.o. ↑ AUC; ↓ $Cl_r$	van Crugten et al., 1986
	Cimetidine	Dofetilide	p.o. ↑ AUC, $C_{max}$ ; ↓ $Cl_r$	Abel et al., 2000
	Cimetidine	Pindolol	p.o. ↑ AUC, $C_{max}$ ; ↓ $Cl_r$	Somogyi et al., 1992
	Trimethoprim	Procainamide	p.o. ↑ AUC; ↓ $Cl_r$	Kosoglou et al., 1988
P-gp	Clarithromycin	Digoxin	p.o. ↑ AUC, $C_{max}$	Rengelshausen et al., 2003; Gurley et al., 2008
	Quinidine	Digoxin	i.v. ↑ $C_{serum}$ ; ↓ $Cl_t$ , $Cl_r$	Leahey et al., 1981; Ochs et al., 1981; Schenck-Gustafsson and Dahlqvist, 1981; Fenster et al., 1982, 1984
	Rifampin	Digoxin	i.v. ↓ AUC, $C_{max}$ ; ↑ $Cl_{nr}$ p.o. ↓ AUC, $C_{max}$ , F	Drescher et al., 2003; Greiner et al., 1999; Larsen et al., 2007; Gurley et al., 2008; Reitman et al., 2011
BCRP	Rifampin	Talinolol	i.v. ↓ AUC, $C_{max}$ ; ↑ $Cl_t$ p.o. ↓ AUC, $C_{max}$ , F; ↑ $t_{max}$ , $Cl_t$	Westphal et al., 2000
	Ritonavir	Digoxin	i.v. ↑ AUC; ↓ $Cl_t$ , $Cl_r$	Ding et al., 2004
	St John's Wort	Digoxin	p.o. ↓ AUC, $C_{max}$ , $C_{trough}$	Gurley et al., 2008; Johne et al., 1999
	St John's Wort	Talinolol	i.v. ↑ $Cl_{nr}$ p.o. ↓ AUC, F	Schwarz et al., 2007
	Topotecan	Elacridar	i.v. ↑ AUC p.o. ↑ AUC, $C_{max}$ , F	Kruijtzter et al., 2002

↑, Significant increase; ↓, significant decrease;  $C_{serum}$ , serum concentration;  $C_{trough}$ , minimum plasma/serum concentration during steady state;  $Cl_r$ , renal clearance;  $Cl_{nr}$ , nonrenal clearance; F, bioavailability; NTCP, sodium/taurocholate cotransporting polypeptide (modified from Müller and Fromm, 2011).

transporters such as the urate transporter URAT1 (Koepsell and Endou, 2004). Members of this family, which are important for drug disposition, include the three organic cation transporters OCT1 (gene symbol *SLC22A1*), OCT2 (*SLC22A2*), and OCT3 (*SLC22A3*)

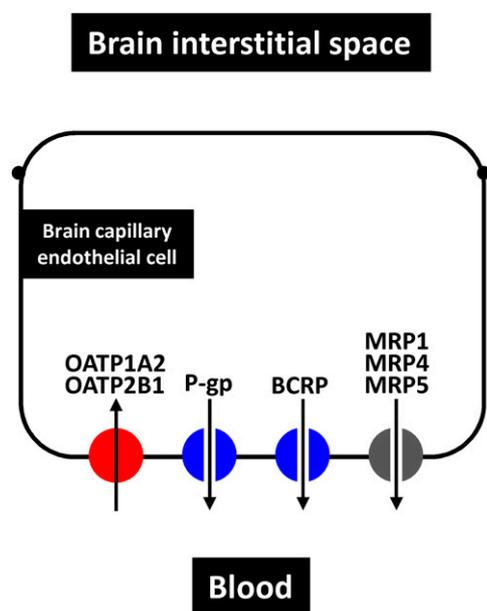


Fig. 4. Transporters expressed in human brain capillary endothelial cells. Uptake transporters discussed in this review are colored in red, export proteins in blue.

as well as the organic anion transporters OAT1 (*SLC22A6*), OAT2 (*SLC22A7*), OAT3 (*SLC22A8*), and OAT4 (*SLC22A11*).

The OCT1 protein exhibits a broad tissue distribution with a high expression in liver [Fig. 2 (Gorboulev et al., 1997)] and weaker expression in some other tissues such as spleen and lung. It is noteworthy that, as demonstrated in hepatocellular carcinoma samples, DNA methylation of the *SLC22A1* gene is associated with the downregulation of OCT1 protein (Schaeffeler et al., 2011), indicating that epigenetic factors influence the expression of transport proteins. OCT2 shows a more restricted expression pattern and is highly expressed in proximal kidney tubule cells (Gorboulev et al., 1997). In contrast to OCT1 and OCT2, which are predominantly expressed in the major excretory organs liver and kidney, respectively, the OCT3 protein shows a broad expression pattern with moderate to high expression in the intestinal epithelium (Nishimura and Naito, 2005), in human hepatocytes (Nies et al., 2009), and in proximal tubule epithelial cells (Nishimura and Naito, 2005).

As shown for the members of the OATP family on the basis of in vitro studies, the three OCTs also share a similar and partially overlapping substrate spectrum. OCT1, OCT2, and OCT3 transport a variety of organic cations with widely differing molecular structures. Furthermore, they are inhibited by several compounds

that are not transported by the respective uptake transporter. The transport is independent of proton or sodium gradients and, as demonstrated so far for OCT1 and OCT2, electrogenic (Gorboulev et al., 1997). The model substrate 1-methyl-4-phenylpyridinium (MPP<sup>+</sup>) exhibits high maximal uptake rates and similar kinetic constants ( $K_m$  values) for all three OCTs (Gorboulev et al., 1997). Furthermore, several endogenous compounds such as neurotransmitters, hormones, and metabolites are transported in vitro by OCTs (for review, see Koepsell et al., 2007). Drugs transported by or inhibiting all three OCTs in vitro include anesthetic drugs [e.g., ketamine and cocaine (Amphoux et al., 2006)],  $\beta$ -blockers [e.g., propranolol (Umehara et al., 2008; Bachmakov et al., 2009)], antidepressants [e.g., citalopram (Ahlin et al., 2008)], and oral antidiabetic drugs [e.g., metformin (Kimura et al., 2005)]; for detailed description of the substrate spectrum of OCT1–OCT3, see Nies et al., 2011].

The anion transporters OAT1 to OAT4 also belong to the *SLC22* family. OAT1 is expressed in different tissues with the highest expression in kidney (Lopez-Nieto et al., 1997) and located there in the basolateral membrane of proximal tubule cells (Fig. 3). In addition, mRNA transcripts of OAT1 have been detected in the brain [cerebellum, hippocampus, and hypothalamus (Cihlar and Ho, 2000)] and the choroid plexus (Sweet et al., 2002). OAT2 is highly expressed in human liver (Sekine et al., 1997) and to a lower extent also in the kidney with the same localization as the OAT1 protein [Fig. 3 (Enomoto et al., 2002)]. Similar to OAT1 and OAT2, OAT3 is also expressed in the kidney and localized in the same membrane domain [Fig. 3 (Cha et al., 2001)]. In contrast to OAT1, which shows the highest expression in the S2 segment, OAT3 was present in all proximal tubule segments (Kojima et al., 2002). Expression of *SLC22A8* mRNA encoding OAT3 was also detected in human brain (Kusuhara et al., 1999) and brain capillaries [Fig. 4 (Ohtsuki et al., 2002)]. Similar to OAT1 to OAT3, OAT4 is also expressed in renal epithelium, but in contrast to these it is localized in the luminal membrane of proximal tubule cells [Fig. 3 (Babu et al., 2002)].

It is assumed that under physiologic conditions all OATs operate as organic anion/dicarboxylate exchangers (Burckhardt and Burckhardt, 2011). All four uptake transporters have a very broad substrate spectrum, with several endogenous metabolites being substrates or inhibitors. These include second messengers [e.g., cGMP as substrates for OAT1–OAT3 (Cropp et al., 2008)], citric acid cycle intermediates (dicarboxylates), bile salts, or hormone derivatives (e.g., estrone-3-sulfate). Furthermore, several drugs have been identified as substrates or inhibitors of OATs. OAT1 is the best characterized OAT with respect to its substrate spectrum [angiotensin-converting enzyme (ACE) inhibitors (e.g., captopril), diuretics (e.g., bumetanide and furosemide), antibiotics

(e.g., ceftibuten) or antivirals (e.g., ganciclovir)]. Interestingly, OAT1 transport can be inhibited by several statins but up to date, no OAT1-mediated statin transport has been detected [for detailed description of the substrate spectrum see (Burckhardt and Burckhardt, 2011; Emami Riedmaier et al., 2012)]. OAT2 shows an overlapping substrate spectrum with OAT1 and OAT2-mediated transport can also be inhibited by statins (Khamdang et al., 2004). For OAT3 ACE inhibitors [e.g., quinapril (Yuan et al., 2009)], angiotensin II receptor blockers [olmesartan (Yamada et al., 2007)], several diuretics, and antibiotics have been characterized as substrates. Interestingly and in contrast to OAT1 and OAT2, OAT3 is capable of transporting rosuvastatin and pravastatin (Hasegawa et al., 2002). In addition, atorvastatin, fluvastatin, pravastatin, rosuvastatin, and simvastatin are inhibitors of OAT3-mediated transport (Khamdang et al., 2004; Windass et al., 2007). For OAT4 only a few drugs have been identified as substrates. These include the diuretics bumetanide (Hasannejad et al., 2004) and torasemide (Hagos et al., 2007) and the antineoplastic agent methotrexate (Takeda et al., 2002b). Several other drugs have been identified as inhibitors of OAT4-mediated uptake.

## B. Efflux Transporters

1. *The MDR/TAP Family (ABC Family ABCB)*. The human multidrug resistance/transporters of antigen presentation (MDR/TAP) family consists of 11 different ABC transporters including the peptide transporters TAP1 and TAP2 (gene symbols *ABCB2* and *ABCB3*), the phospholipid translocator MDR3 (*ABCB4*), the drug export pump P-gp (*MDR1, ABCB1*), and the bile salt export pump BSEP (*ABCB11*). Both latter ones are important for drug disposition and therefore in the focus of this review.

P-gp is the most studied export pump mediating the transport of drugs and drug conjugates from the intracellular to the extracellular space. It is expressed in several tissues including intestine, kidney, liver, brain (Figs. 1–4), and placenta. It is located at the apical side of the barriers mediating the inside-out extrusion of different exogenous and xenobiotic compounds. P-gp is expressed in the apical membrane of the entire intestine from duodenum to rectum (Canaparo et al., 2007), with a high expression in enterocytes of the small intestine thereby contributing to a reduced bioavailability of multiple drugs that are substrates of this transporter. In hepatocytes P-gp is located in the canalicular membrane (Thiebaut et al., 1987) and in the kidney at the luminal side of proximal tubule epithelial cells [Figs. 2 and 3 (Thiebaut et al., 1987)] mediating the export of xenobiotics into bile and urine, respectively. P-gp is also important for the blood-brain barrier (Fromm, 2000) as a defense mechanism against the penetration of toxins and drugs into the central nervous system (CNS).

P-gp has a very wide substrate spectrum mediating the export of a variety of drugs from different drug classes. Substrates include anticancer drugs (e.g., docetaxel, etoposide, vincristine), immunosuppressants [e.g., cyclosporine (CsA), tacrolimus], antibiotics (e.g., macrolides), statins (e.g., atorvastatin, lovastatin), cardiac drugs (e.g., digoxin, digitoxin), and  $\beta$ -blockers (e.g., carvedilol; for detailed description of the substrate spectrum, see Fromm, 2004; Cascorbi and Haenisch, 2010). Because of its localization at membrane barriers and its wide substrate spectrum, P-gp is an important determinant of pharmacokinetics and an important mediator of transporter-mediated drug-drug interactions (see section III.D).

The second MDR1/TAP family member, which is in particular important for drug side effects via inhibition of this transporter, is the bile salt export pump BSEP. BSEP shows the highest expression in liver and is located in the canalicular membrane of hepatocytes. BSEP, initially termed "sister of P-glycoprotein" (Gerloff et al., 1998), catalyzes the export of conjugated and unconjugated bile salts into bile, therefore being responsible for the bile-salt-dependent bile flow (Noe et al., 2005). On the basis of this important function, inhibition of BSEP can lead to impaired bile flow and cholestasis. Furthermore, it has been demonstrated that BSEP may also transport non-bile acid compounds such as pravastatin (Hirano et al., 2005a) and that the transport of bile acids can be inhibited by several drugs such as CsA, rifampin, vinblastine, and troglitazone (Yabuuchi et al., 2008).

**2. The MRP2 Protein (ABC Family ABCC).** The human MRP family consists of 9 MRP proteins (MRP1–MRP9, gene symbols *ABCC1–ABCC6* and *ABCC10–ABCC12*), the cystic fibrosis transmembrane conductance regulator (*ABCC7*) protein, and the SUR proteins SUR1 and SUR2 (sulfonylurea receptor, *ABCC8* and *ABCC9*). The apically localized export pump MRP2 (*ABCC2*) seems to be the most important member of this family for drug disposition.

MRP2 represents an apically localized export pump of the MRP family and is highly expressed in liver (Büchler et al., 1996), kidney (Schaub et al., 1999), small intestine [Figs. 1–3 (Fromm et al., 2000)], gall bladder (Rost et al., 2001), and placenta (St-Pierre et al., 2000). The exclusively apical localization is in line with its role for the excretion of many phase II metabolites of drugs and endogenous compounds into bile, urine, and the intestinal lumen.

Substrates of MRP2 characterized by in vitro studies include endogenously synthesized metabolites such as mono- and bisglucuronosyl bilirubin (Kamisako et al., 1999), 17 $\beta$ -glucuronosyl estradiol (Cui et al., 1999), or the glutathione conjugate leukotriene C<sub>4</sub> (Cui et al., 1999). Furthermore, several drugs and drug metabolites have been identified as substrates, including chemotherapeutic agents such as methotrexate (Masuda

et al., 1997) or melphalan (Barnouin et al., 1998) and statins [e.g., pravastatin (Yamazaki et al., 1997)]. A detailed description of the substrate spectrum can be found in other reviews (Nies and Keppler, 2007; Keppler, 2011).

**3. The BCRP Protein (ABC Family ABCG).** Breast cancer resistance protein (BCRP, gene symbol *ABCG2*) is a member of the ABCG family of ABC transporters. This so-called half-size ABC transporter (Table 1) is expressed in different tissues including intestine, liver, kidney, and brain (Figs. 1–4) and in addition in testis and placenta (Maliepaard et al., 2001). In enterocytes, hepatocytes, proximal tubule epithelial cells, and brain capillary endothelial cells BCRP is localized to the apical/luminal membrane. Several drugs have been identified as substrates and/or inhibitors of BCRP by means of in vitro studies. Substrates include antivirals [e.g., acyclovir (Jonker et al., 2005)], statins [e.g., pravastatin (Matsushima et al., 2005) and rosuvastatin (Huang et al., 2006)], anticancer drugs [e.g., topotecan (Maliepaard et al., 1999)], antibiotics [e.g., ciprofloxacin and ofloxacin (Ando et al., 2007)], as well as diclofenac (Lagas et al., 2009), sulfasalazine (van der Heijden et al., 2004), and cimetidine (Jonker et al., 2005). Furthermore, endogenous substances and metabolites such as vitamin K<sub>3</sub> (Shukla et al., 2007), estrone-3-sulfate, dehydroepiandrosterone sulfate (Suzuki et al., 2003), and uric acid (Woodward et al., 2009) have been shown to be transported by BCRP. Substances that inhibit BCRP-mediated export in vitro without being transported itself include cyclosporine (Gupta et al., 2006), omeprazole and pantoprazole (Breedveld et al., 2004), saquinavir (Gupta et al., 2004), and tacrolimus (Gupta et al., 2006).

**4. The MATE Family (SLC Family SLC47).** The *SLC47A1* cDNA encoding human MATE1 was identified in 2005 (Otsuka et al., 2005) as the human ortholog of the bacterial NorM transporter, suggesting that also MATE1 is an H<sup>+</sup>/organic cation antiporter (Terada et al., 2006). This was functionally established using HEK293 cells recombinantly overexpressing MATE1 (Otsuka et al., 2005). The *SLC47A2* cDNA encoding human MATE2-K (also termed MATE2) was cloned subsequently as a homolog of human MATE1 (Masuda et al., 2006). Whereas MATE1 is expressed in both liver and kidney, MATE2-K is highly expressed in kidney and to lower levels also in colon and testis. MATE1 is localized in the canalicular membrane of hepatocytes (Otsuka et al., 2005) and together with MATE2-K in the luminal membrane of proximal tubule epithelial cells [Figs. 2 and 3 (Masuda et al., 2006)].

On the basis of in vitro studies, MATE1 and MATE2-K have similar inhibitor and substrate specificities partially overlapping with those of OCTs (for summary, see Damme et al., 2011; Nies et al., 2011). Endogenous substrates of both transporters include the organic cations guanidine, thiamine, *N*-methylnicotinamide (NMN), and creatinine. Today, more than 30

clinically relevant drugs have been identified as inhibitors or substrates of MATE1 and MATE2-K, including cimetidine, acyclovir, metformin, the antiarrhythmic drug procainamide, and the antineoplastic agent topotecan.

### III. Drug-Drug Interactions

*A. Members of the OATP Family.* A variety of drugs have been identified as substrates for the four OATP family members OATP1A2, OATP1B1, OATP1B3, and OATP2B1 expressed in organs important for drug disposition and effects (Figs. 1 and 2). Interestingly, it has been demonstrated that these OATPs share a similar and partially overlapping substrate spectrum. Bromosulfophthalein is transported by all four OATPs with low  $K_m$  values of 20, 0.1, 3.3, and 0.7  $\mu\text{M}$  for OATP1A2, OATP1B1, OATP1B3, and OATP2B1, respectively (König et al., 2000b; Cui et al., 2001; Kullak-Ublick et al., 2001). Therefore, bromosulfophthalein is often used as model substrate for in vitro interaction studies using drugs as potential transport modulators.

The best characterized family members regarding clinical relevance are OATP1B1 and OATP1B3, which are both mentioned in the EMA guideline (EMA, 2012) and the FDA draft guidance for the investigations of drug interactions ([www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm292362.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm292362.pdf)). Because OATP1B1 and OATP1B3, which are believed to have similar functions such as rodent *Oatp1b2*, have no direct orthologous proteins in rodents (König et al., 2000a), in vitro studies using stably transfected cell systems are an important model to study drug interactions with these transporters. Selected in vitro inhibitors of OATP-mediated transport are summarized in Table 2, and examples of clinically relevant drug-drug interactions with a contribution of OATPs are shown in Table 3.

The largest body of evidence for a role of OATPs for drug-drug interactions is available for statins (Kalliokoski and Niemi, 2009). It should be noted that statins considerably differ in the affinity to drug-metabolizing enzymes and uptake/efflux transporters. Atorvastatin and simvastatin are metabolized by CYP3A4, fluvastatin by CYP2C9, whereas metabolism plays a minor role for pitavastatin and rosuvastatin and pravastatin is not metabolized by cytochrome P450 enzymes (Neuvonen et al., 2008; Elsby et al., 2012).

All statins are substrates for OATP1B1 and OATP1B3, and genetic variations in genes encoding these uptake transporters (single nucleotide polymorphisms) affect disposition of all statins except of fluvastatin (Niemi et al., 2011; Elsby et al., 2012). Other hepatic uptake transporters [OATP2B1 (Grube et al., 2006), the sodium/taurocholate cotransporting polypeptide NTCP (Ho et al., 2006)] can contribute to the disposition of statins. Moreover, in vitro and partially in vivo statins have

been characterized as substrates of efflux transporters such as BCRP (Hirano et al., 2005b), P-gp (Chen et al., 2005), and MRP2 (Niemi et al., 2006).

Because OATP-mediated statin uptake in hepatocytes is a prerequisite for their subsequent action as inhibitors of the HMG-CoA reductase, inhibition of this uptake (e.g., by a concomitantly administered drug that is also a substrate for the respective uptake transporter) may contribute to an increase in statin plasma concentrations with the risk of side effects such as myopathy and rhabdomyolysis. Multiple interaction studies using statins as substrates for transporters have been conducted (for reviews, see Kalliokoski and Niemi, 2009; Neuvonen, 2010; Niemi et al., 2011).

A potent inhibitor of OATP-mediated statin transport is CsA. For OATP1B1-mediated pitavastatin or rosuvastatin transport,  $\text{IC}_{50}$  values of 0.24  $\mu\text{M}$  (Hirano et al., 2004) and 0.31  $\mu\text{M}$  (Ho et al., 2006) have been calculated, respectively. CsA also inhibited OATP1B3-mediated rosuvastatin transport with an  $\text{IC}_{50}$  value of 0.06  $\mu\text{M}$  (Ho et al., 2006), demonstrating that CsA is a very potent inhibitor of OATP-mediated transport. Interestingly, it has recently been demonstrated that the mechanism behind this inhibition is a long-lasting effect of CsA on OATP-mediated uptake with a measurable reduction of OATP1B1 activity for at least 18 hours after its removal from the uptake assay (Shitara et al., 2012).

The effect of CsA on statin disposition has also been investigated in vivo. For example, Hedman et al. (2004) investigated pharmacokinetics and short-term safety of pravastatin in children undergoing triple-drug (including cyclosporine) immunosuppressive therapy after cardiac transplantation. The authors found that the  $C_{\text{max}}$  and AUC of pravastatin were  $122.2 \pm 88.2 \text{ ng/ml}$  and  $264.1 \pm 192.4 \text{ ng} \times \text{h/ml}$ , respectively, and these values were nearly 10-fold higher than the corresponding values reported in children with hypercholesterolemia who were receiving the same pravastatin dose in the absence of immunosuppressive therapy. Because pravastatin is not metabolized, this increase is likely to be attributed to the inhibition of hepatic uptake transporters. These results confirmed results of an earlier study performed in patients who underwent kidney transplantation and are receiving pravastatin or lovastatin together with CsA [Table 3 (Olbricht et al., 1997)]. It is noteworthy that, in this study, it was demonstrated that pravastatin coadministered with CsA did not accumulate over the study period, even if the AUC was 5-fold higher than values reported in the absence of CsA (AUC for single dose at day one:  $249 \mu\text{g} \times \text{h/ml}$ , AUC for multiple doses after 28 days:  $241 \mu\text{g} \times \text{h/ml}$ ), whereas lovastatin accumulated over time in CsA-treated patients (AUC for single dose at day one:  $243 \mu\text{g} \times \text{h/ml}$ , AUC for multiple doses after 28 days:  $459 \mu\text{g} \times \text{h/ml}$ ). This is probably one of the reasons that rhabdomyolysis appears

to be less frequent in pravastatin-treated patients with CsA than in patients with lovastatin and CsA (Olbricht et al., 1997).

The interaction of rosuvastatin with CsA was investigated in a study with 10 stable patients who underwent heart transplantation (Simonson et al., 2004) and were taking 10 mg of rosuvastatin for 10 days. Compared with control patients without CsA, the AUC and the  $C_{\max}$  in the patients who had undergone transplantation were increased 7.1- and 10.6-fold, respectively (Table 3). In the same study, oocytes expressing OATP1B1 were used for inhibition experiments. The  $IC_{50}$  value for the inhibition of rosuvastatin uptake by CsA was 2.2  $\mu\text{M}$  (Simonson et al., 2004), demonstrating the in vitro potency of CsA on inhibiting uptake transporters. The interaction of pitavastatin with CsA was investigated in six healthy volunteers, demonstrating that the coadministration of both drugs led to a 4.5- and 6.6-fold increase in AUC and  $C_{\max}$ , respectively (Hasunuma et al., 2003).

The antituberculosis drug rifampin is a known inducer of drug-metabolizing enzymes and an inhibitor of OATP1B1 and OATP1B3 in vitro (Vavricka et al., 2002; Tirona et al., 2003). In one study in healthy volunteers, it was shown that a single dose of rifampin (600 mg) raised the AUC of coadministered atorvastatin by more than 600% (Lau et al., 2007), probably by inhibiting OATP-mediated hepatic uptake of atorvastatin. It is noteworthy that, for the same drug combination, a genotype-dependent interaction was detected (see section VI).

By use of HEK293 cells stably overexpressing OATP1B1 and OATP1B3, it could be demonstrated that several widely prescribed oral antidiabetic drugs inhibited OATP-mediated pravastatin (Bachmakov et al., 2008) and atorvastatin uptake (Klatt et al., 2013). It is noteworthy that rosiglitazone at the lowest tested concentration of 10  $\mu\text{M}$  significantly inhibited OATP1B1- and OATP1B3-mediated atorvastatin uptake, whereas under the same experimental conditions, the uptake of pravastatin was stimulated, suggesting that not only uptake inhibition but also the stimulation of transport could be considered as a potential mechanism of transporter-mediated drug-drug interactions. This stimulating effect has also been demonstrated in vitro for the interaction of pravastatin with several nonsteroidal anti-inflammatory drugs (Kindla et al., 2011). In this study, the authors demonstrated that OATP1B1- and OATP1B3-mediated pravastatin uptake was stimulated by coadministered diclofenac, ibuprofen, or lumiracoxib with half-maximal effective concentrations ( $EC_{50}$  values) of 64.0 and 93.1  $\mu\text{M}$  for ibuprofen-induced stimulation of OATP1B1- and OATP1B3-mediated pravastatin uptake, respectively. The clinical relevance of these findings is unknown at present.

The interaction of the oral antidiabetic drug repaglinide with CsA was investigated in vivo. In a randomized

crossover study with 12 healthy volunteers, it was demonstrated that in the CsA phase the mean peak repaglinide plasma concentration was 175% and the AUC was 244% of that measured in the placebo phase with repaglinide given alone (Kajosaari et al., 2005). In the same study, a genotype-dependent effect of CsA on the AUC of repaglinide was detected (see section VI).

According to the US FDA Adverse Event Reporting System, eight cases (with one death) of rhabdomyolysis were reported between October 1997 and December 2000 for the concomitant pravastatin and fibrate therapy (Igel et al., 2002). To further investigate this interaction, a study was performed in which 10 healthy volunteers took gemfibrozil (1200 mg/day) or placebo for 3 days. On day 3, each subject ingested a single dose (40 mg) of pravastatin. These experiments demonstrated that during the gemfibrozil phase, the mean AUC of pravastatin was 202% of that during the placebo phase. This interaction may represent an interference of gemfibrozil and/or its glucuronide [both known inhibitors of OATP1B1-mediated transport (Shitara et al., 2004)] with the hepatic uptake of pravastatin mediated by OATP1B1 and OATP1B3.

Macrolides are known to cause severe drug-drug interactions, and in most cases analyzed so far, these interactions have been attributed to the inhibition of metabolizing enzymes. Nevertheless, several studies have investigated the effect of macrolides on OATP-mediated uptake in vitro or on the disposition of OATP substrates in humans. Seithel et al. (2007) demonstrated in vitro that pravastatin transport can be inhibited by the simultaneous application of clarithromycin or roxithromycin. In humans, clarithromycin increases the  $C_{\max}$  values of the CYP3A4 and OATP1B1 substrates simvastatin and atorvastatin by 609 and 446%, respectively (Jacobson, 2004). It is noteworthy that, in the same study, it was demonstrated that clarithromycin also increases  $C_{\max}$  of coadministered pravastatin from 18 to 41 ng/ml and the AUC from 54 to 114 ng  $\times$  h/ml, suggesting that this observed interaction may be attributable to the inhibition of OATP-mediated pravastatin uptake into hepatocytes resulting in increased plasma concentrations.

For the endothelin receptor antagonist bosentan, which is mainly metabolized by CYP2C9 and CYP3A4 and transported by OATP1B1 and OATP1B3 (Treiber et al., 2007), it has been reported that coadministration of CsA, ketoconazole, rifampin, or sildenafil increased the plasma concentrations of bosentan in humans (van Giersbergen et al., 2002; Treiber et al., 2007). Detailed analysis of bosentan transport inhibition demonstrated that sildenafil inhibited OATP1B1- and OATP1B3-mediated bosentan uptake with  $IC_{50}$  values of 1.5 and 0.8  $\mu\text{M}$ , respectively. Because sildenafil is not an inhibitor of CYP2C9 and CYP3A4, inhibition of uptake transporters may be the major determinant of this drug-drug interaction.

For the interpretation of clinical drug-drug interaction studies, it should be kept in mind that several inhibitors of OATPs (e.g., CsA) are also potent inhibitors not only of drug-metabolizing enzymes but also of other transport proteins (MRP2, P-gp). Very recently, an interesting review was published estimating the theoretical maximum fold increase in statin AUCs if single, dual, or triple pathways of metabolism and transport are inhibited (Elsby et al., 2012).

**B. Members of the OAT Family.** Although OATs are present in various tissues (see section II.A.2), the examination of drug-drug interactions attributable to OAT inhibition has so far concentrated on the kidney. In particular, OAT1 and OAT3, as facilitators of the basolateral uptake of anionic drugs into proximal renal tubular cells (Fig. 3), are thought to be involved in several drug-drug interactions [Tables 2 and 3 (Lepist and Ray, 2012)]. The substrate spectra of both transporters are broad and partially overlapping, including drugs such as antibiotics, antivirals, or H<sub>2</sub>-receptor antagonists (Burckhardt and Burckhardt, 2011). A well-characterized substrate of OAT3 is the antibiotic benzylpenicillin [ $K_m$  value of 54  $\mu\text{M}$  (Deguchi et al., 2004)]. Animal experiments support the importance of OAT3 for benzylpenicillin pharmacokinetics: VanWert et al. (2007) reported that in *mOat3(-/-)* knockout mice the antibiotic's plasma AUC and elimination half-life were increased compared with *Oat3* expressing mice (VanWert et al., 2007). The antivirals acyclovir and cidofovir, on the other hand, were transported by OAT1 ( $K_m$  values of 342 and 46–58  $\mu\text{M}$ ), whereas no (acyclovir) or only weak (cidofovir) transport was found for OAT3 (Cihlar et al., 1999; Ho et al., 2000; Cha et al., 2001; Takeda et al., 2002a; Uwai et al., 2007). Both OAT1 and OAT3 were reported to transport the loop diuretic furosemide and the antineoplastic agent methotrexate, although for the latter, absence of OAT1-mediated uptake using low concentrations has been reported as well (Lu et al., 1999; Hasannejad et al., 2004; Uwai et al., 2004). Detailed lists of OAT substrates and inhibitors have been published in a recent review article (Burckhardt and Burckhardt, 2011).

A well-characterized inhibitor of both OAT1 and OAT3 is probenecid. Today, probenecid is only rarely used in therapy, but it provides an excellent example for drug-drug interactions mediated by OAT inhibition. Both OAT1 and OAT3 are inhibited by probenecid with similar affinities [ $K_i$  values of 4.3–12.1 and 1.3–9.0  $\mu\text{M}$  for OAT1 and OAT3, respectively (Jung et al., 2001; Takeda et al., 2001; Hashimoto et al., 2004; Tahara et al., 2005)]. Those  $K_i$  values are smaller than the therapeutic unbound probenecid plasma concentration [18.7  $\mu\text{M}$  (Nozaki et al., 2007)]. The drug was initially used to decrease the renal tubular secretion of antibiotics, especially benzylpenicillin, to prolong their elimination half-life and increase serum concentrations (Burnell and Kirby, 1951). The need to raise serum

concentrations of benzylpenicillin was mainly attributable to limited supplies of antibiotics during and shortly after World War II (Robbins et al., 2012). Because of its uricosuric properties mediated by inhibition of renal tubular reabsorption of urate, probenecid was also standard of care for prevention of gout symptoms in predisposed patients (Robbins et al., 2012). However, with new therapies such as allopurinol becoming available, the importance of probenecid in the therapy of gout has declined.

Nowadays, probenecid is regularly used during treatment with cidofovir. The use of this antiviral is limited by its severe nephrotoxicity, and uptake of cidofovir by proximal renal tubule cells is a prerequisite for development of kidney damage (Izzedine et al., 2005; Ortiz et al., 2005). There is evidence that OAT1-mediated uptake by renal tubular cells plays a crucial role in cidofovir's nephrotoxicity. Expressed in Chinese Hamster ovary cells, probenecid inhibits both OAT1-mediated uptake and cytotoxicity of cidofovir (Ho et al., 2000). Therefore, in therapy, high doses of probenecid are regularly coadministered with cidofovir to improve renal tolerability of the drug (Lalezari et al., 1995; Lacy et al., 1998; Izzedine et al., 2005).

In clinical studies, probenecid also affected the pharmacokinetics of other OAT substrates. For example, coadministration of probenecid decreased the renal clearance and increased elimination half-time and plasma concentrations of intravenously or orally administered furosemide in healthy volunteers (Homeida et al., 1977; Honari et al., 1977; Odland and Beermann, 1980; Smith et al., 1980; Vree et al., 1995). Another example is the antineoplastic agent methotrexate. In patients, probenecid increased both methotrexate's elimination half-time and plasma concentrations (Aherne et al., 1978; Lilly and Omura, 1985).

Another OAT inhibitor is the fibrate gemfibrozil. Nakagomi-Hagihara et al. (2007) reported that gemfibrozil and two of its metabolites inhibited in vitro OAT3-mediated uptake of pravastatin with a potentially clinically relevant potency. Inhibition of OAT3 may partly contribute to the interaction of gemfibrozil with the OAT3 substrate pravastatin that has been observed in vivo. As described in section III.A, in 10 healthy volunteers gemfibrozil increased pravastatin plasma concentrations, and the underlying mechanism is thought to be inhibition of hepatic uptake transporters (Kyrklund et al., 2003). However, in this study, gemfibrozil also decreased renal pravastatin clearance by 43%, and it is likely that OAT3 inhibition underlies the renal component of this interaction (Kyrklund et al., 2003; Watanabe et al., 2003). Coadministration with gemfibrozil also increased plasma concentrations of the dipeptidyl peptidase IV (DPP-IV) inhibitor sitagliptin (Arun et al., 2012). Sitagliptin is mainly eliminated by renal excretion of the unchanged substance with a significant contribution of tubular secretion (Herman

et al., 2005; Scheen, 2007). In vitro, sitagliptin is transported by several transporters including OAT3 (Chu et al., 2007) and P-gp, and it is possible that inhibition of renal OAT3 by gemfibrozil and its metabolites contributes relevantly to this interaction (see also Supplemental Table 1 for respective information in SPCs).

*C. Members of the OCT Family and the MATE Family.* In the liver, basolateral OCT1 and OCT3 mediate the uptake of their substrates from the sinusoidal blood into hepatocytes, whereas MATE1 in the apical membrane is thought to export drugs into the bile [Fig. 2 (Damme et al., 2011)]. In renal proximal tubule cells, OCT2, MATE1 and MATE2-K are thought to be important components of the renal tubular secretory system for basic drugs [Fig. 3 (Yonezawa and Inui, 2011a)]. The drug most intensively studied as substrate of OCTs and MATEs is the antidiabetic metformin. Because of its high  $pK_a$  (>99.99% are positively charged at pH 7.4) and its negative  $\log P$  value, passive diffusion of metformin through cellular membranes is minimal. Therewith, transport by drug transporters is pivotal for the permeation of metformin through cellular membranes. The apparent  $K_m$  values reported for the transport of metformin by OCTs and MATEs are relatively high, ranging between 253  $\mu\text{M}$  [MATE1 (Kusuhara et al., 2011)] and 2260  $\mu\text{M}$  [OCT3 (Nies et al., 2009)]. Lists of OCT and MATE substrates and inhibitors have been compiled in recent reviews (Damme et al., 2011; Nies et al., 2011), and selected inhibitors and drug-drug interactions are shown in Tables 2 and 3.

The  $H_2$ -receptor antagonist cimetidine was first identified as an inhibitor of OCTs; however, its affinity toward MATEs seems to be higher.  $K_i$  values reported for inhibition of MATE1- or MATE2-K-mediated transport range between 1.1 and 7.3  $\mu\text{M}$  (Tsuda et al., 2009b; Higgins et al., 2012), whereas for OCTs  $K_i$  values are 101–166  $\mu\text{M}$  (OCT1) and 95–724  $\mu\text{M}$  [OCT2 (Zhang et al., 1998; Lee et al., 2009; Ito et al., 2012b)]. An even more potent inhibitor of MATEs is the antiprotozoal pyrimethamine with  $K_i$  values of 77–93 nM (MATE1) and 46–59 nM [MATE2-K (Zhang et al., 1998; Kusuhara et al., 2011; Ito et al., 2012b)]. The  $K_i$  values of pyrimethamine for inhibition of OCTs are orders of magnitude higher (OCT1: 3.8  $\mu\text{M}$ ; OCT2: 10  $\mu\text{M}$ ), making the antiprotozoal a preferential inhibitor of MATEs (Ito et al., 2010).

Another class of drugs with potent inhibitory effects on OCTs and MATEs are tyrosine kinase inhibitors (TKIs). Minematsu and Giacomini (2011) reported that imatinib and erlotinib inhibited metformin uptake by MATE1 and OCT1, respectively, with  $IC_{50}$  values that are exceeded by the maximal unbound drug concentrations during therapy.

The interactions between cimetidine or pyrimethamine and different substrates of OCTs and MATEs

have been examined in vivo in mouse experiments that further increased our understanding of drug-drug interactions on the level of these transporters. The tissue distribution of the transporters varies between species, but substrate and inhibitor spectra are comparable. It is noteworthy that  $K_i$  values of cimetidine and pyrimethamine for mouse and human OCTs and MATEs are in similar ranges in both species (Ito et al., 2010, 2012b). In mice, metformin is taken up into hepatocytes via mOct1 and secreted into bile by mMate1, in kidney mOct1 and mOct2 in the basolateral membrane and mMate1 in the luminal membrane of renal proximal tubule cells mediate metformin secretion into the urine (Tsuda et al., 2009a; Higgins et al., 2012). Coinfusion of cimetidine increases metformin concentrations in mouse kidney and liver, probably because of inhibition of mMate1-mediated metformin export (Ito et al., 2012b). This suggests that cimetidine exerts its interactions preferentially via inhibition of MATEs rather than by inhibition of OCT-mediated transport.

On the other hand, cimetidine protects mice from cisplatin toxicity. Cisplatin is a platinum-based anticancer drug, the use of which is limited by severe nephrotoxicity, and OCT2-mediated uptake into proximal renal tubule cells seems to play a major role in the development of renal damage attributable to its use (Ciarimboli et al., 2005; Filipinski et al., 2009; Yonezawa and Inui, 2011b; Iwata et al., 2012). Coadministration of cimetidine with intraperitoneally applied cisplatin protects mice not only partially from nephrotoxicity but also from damage of the inner ear. These protective effects are attributed to inhibition of mOct-mediated uptake into proximal renal tubule cells and cochlear hair cells, which suggest that cimetidine may also exert relevant inhibition of mOcts (Franke et al., 2010; Ciarimboli et al., 2011).

Ito et al. (2010) also examined the effect of the preferential MATE inhibitor pyrimethamine on the pharmacokinetics of tetraethylammonium and metformin in mice. In line with inhibition of mMate1-mediated export, estimated unbound concentrations up to 30, 150, and 50 nM pyrimethamine in plasma, kidney, and liver, respectively, dose-dependently increased tetraethylammonium kidney-to-plasma concentration ratios from 6.2 to 17 ml/g kidney. Metformin kidney and liver concentration ratios were increased by 3.7- and 2.6-fold, respectively (Ito et al., 2010).

Most drug-drug interactions observed in humans that are attributed to inhibition of OCTs and/or MATEs are caused by cimetidine. After oral administration of 400 mg three times daily for 7 days, cimetidine steady-state unbound plasma concentrations were between approximately 0.7  $\mu\text{M}$  (trough concentration) and 9  $\mu\text{M}$  ( $C_{\text{max}}$ ), which is in the range of reported  $K_i$  values for MATE1 and MATE2-K inhibition and below reported  $K_i$  values for inhibition of OCTs (Kirch et al., 1989). The first report of a drug-drug interaction attributed to

inhibition of the renal tubular secretory system for organic bases was published in 1982 by Somogyi and Heinzow (1982), who examined the effect of cimetidine on the pharmacokinetics of the antiarrhythmic drug procainamide. Procainamide is a basic drug that is eliminated to a substantial degree by renal tubular secretion (Reidenberg et al., 1980). In six healthy volunteers, cimetidine decreased procainamide renal clearance over a 12-hour period from 347 to 196 ml/min, thereby increasing its AUC<sub>0-12</sub> by 35% (Somogyi and Heinzow, 1982; Somogyi et al., 1983).

In another study, Somogyi et al. (1987) examined the interaction between cimetidine and metformin. In humans, metformin is eliminated mainly by renal excretion of the unchanged substance. With an estimated population mean of  $507 \pm 129$  ml/min, metformin renal clearance exceeds glomerular filtration rate by severalfold, which is likely to be attributed to extensive renal tubular secretion (Graham et al., 2011). In the study by Somogyi et al., coadministration of cimetidine (400 mg twice daily) in seven healthy subjects increased the metformin (250 mg once daily)  $C_{\max}$  and AUC<sub>0-24hours</sub> by 81 and 50%, respectively, and decreased its renal clearance over 24 hours by 27% (Somogyi et al., 1987).

In humans, coadministration of cimetidine also caused increased plasma concentrations and reduced renal clearance of the H<sub>2</sub>-receptor antagonist ranitidine, the antiarrhythmic drug dofetilide, the  $\beta$ -blocker pindolol, and the nicotinic acetylcholine receptor partial agonist varenicline [Table 3 (van Crugten et al., 1986; Somogyi et al., 1992; Abel et al., 2000; Feng et al., 2008)].

Recently, Kusuhara et al. (2011) reported a clinical study that examined the effect of pyrimethamine on metformin pharmacokinetics. In eight healthy volunteers, a single oral dose of 50 mg of pyrimethamine reduced the renal clearance of the antidiabetic when it was given at microdose (100  $\mu$ g) or at therapeutic dose (250 mg) by 23 and 35%, respectively. In this study, the plasma concentrations of the endogenous metabolite *N*-methylnicotinamide (NMN) were determined as well. NMN is a substrate of OCT2, MATE1, and MATE2-K, and NMN renal clearance was drastically reduced from 403 to 119 ml/min/kg when pyrimethamine was administered, probably by inhibition of MATE-mediated renal secretion (Ito et al., 2012a). It is possible that the determination of endogenous compounds such as NMN may be a valuable tool to predict drug-drug interactions via inhibition of OCT2 and/or MATEs (Fromm, 2012).

**D. P-Glycoprotein.** Numerous drugs have been identified as P-gp substrates, among them the cardiac glycoside digoxin, human immunodeficiency virus protease inhibitors, immunosuppressants,  $\beta$ -blockers, and anticancer agents (Fromm, 2004; Ho and Kim, 2005; Shitara et al., 2005; Cascorbi, 2011). P-gp substrates are usually hydrophobic molecules with cationic properties

(Giacomini et al., 2010). They can be divided into a few drugs, which are not metabolized in humans and which are considered as probe drugs for P-gp function, such as digoxin, dabigatran etexilate, fexofenadine (EMA, 2012), and talinolol (Oswald et al., 2011), and into the majority of drugs, which are substrates of both P-gp and CYP3A4 and/or other drug-metabolizing enzymes. Selected in vitro inhibitors of P-gp are listed in Table 2, and selected P-gp-mediated drug-drug interactions are shown in Table 3.

Digoxin has an oral bioavailability of 70% and is excreted by glomerular filtration and renal secretion. The largest effects of P-gp inhibitors on digoxin AUC in humans were observed for valsopodar, followed by quinidine, cyclosporine, itraconazole, and clarithromycin (Fenner et al., 2009). Coadministration of quinidine has been shown to increase digoxin bioavailability, to decrease digoxin biliary elimination, and to reduce renal secretion of the cardiac glycoside (Hager et al., 1979; Pedersen et al., 1983; Angelin et al., 1987), most likely by P-gp inhibition in the small intestine, the liver, and the kidney.

This is in line with in vitro studies using Caco-2 cells showing that quinidine reduces polarized, basal-to-apical translocation of digoxin with an IC<sub>50</sub> value of 2.2  $\mu$ M (Fromm et al., 1999; Wandel et al., 1999) and with studies in P-gp-expressing and P-gp-deficient mice, in which an effect of quinidine on digoxin plasma concentrations was detectable in P-gp-expressing mice but not in P-gp-deficient mice (Fromm et al., 1999). Schinkel et al. (1997) reported that 16% of an intravenously administered digoxin dose was eliminated within 90 minutes directly into the intestine in P-gp-expressing mice, whereas this number was reduced to 1.5% in P-gp-knockout [mdr1a/1b(-/-)] mice without P-gp expression. By use of a multilumen perfusion catheter, Drescher et al. (2003) showed in healthy volunteers that luminal quinidine (103.6  $\mu$ M) reduces the direct intestinal secretion into a 20-cm intestinal segment after intravenous administration of digoxin from 0.45% of the digoxin dose to 0.23%. This catheter was also used in combination with stable isotope technology to investigate the influence of luminal quinidine on absorption of lumenally administered digoxin (Igel et al., 2007). Perfusion of one of the segments with quinidine increased digoxin absorption from 22.3 to 55.8% with corresponding changes of the plasma AUC values. Taken together, quinidine inhibits intestinal P-gp, thereby increasing digoxin absorption and bioavailability.

Changes in pharmacokinetic parameters, including renal clearance of digoxin, have been observed in humans after coadministration of multiple other drugs [Table 3 (Fenner et al., 2009)]. It is noteworthy that the EMA recommended in their recent *Guideline on the Investigation of Drug Interactions* (EMA, 2012) to check digoxin renal clearance if renal P-gp inhibition needs to be tested for a new molecular entity. For inhibition

of intestinal P-gp, it is recommended to use low bioavailability drugs, such as the oral anticoagulant dabigatran etexilate or the H<sub>1</sub> antagonist fexofenadine, if no OATP1B1 or OATP1B3 inhibition is expected (EMA, 2012).

P-gp is probably also the transporter with the highest relevance of all transporters for CNS entry of xenobiotics (Fig. 4). In particular, experiments using P-gp-deficient mice highlighted that this transporter limits the CNS entry of multiple drugs [e.g., human immunodeficiency virus protease inhibitors (Kim et al., 1998)]. Sadeque et al. (2000) showed in healthy volunteers that inhibition of P-gp expressed in the blood-brain barrier by quinidine leads to respiratory depression caused by the opioid and P-gp substrate loperamide, whereas no respiratory depression was observed after administration of loperamide without quinidine. There are now multiple studies investigating P-gp function in the blood-brain barrier using positron emission tomography scanning [e.g., with [<sup>11</sup>C]verapamil (Takano et al., 2006)]. For example, Muzi et al. (2009) were able to show using this technology that the P-gp inhibitor cyclosporine increases CNS accumulation of the P-gp substrate verapamil. The clinical relevance of other transporters expressed in the blood-brain barrier for drug-drug interactions requires further studies.

It should be noted that most P-gp substrates are also substrates of drug-metabolizing enzymes such as CYP3A4 (Fromm, 2004). Because many P-gp substrates are also substrates of CYP3A4 and because P-gp inhibitors are also inhibitors of CYP3A4, many of the observed drug-drug interactions are caused by inhibition of both P-gp and CYP3A4 (e.g., with cyclosporine or tacrolimus as victim drugs). The relative importance of P-gp inhibition versus CYP3A4 inhibition needs to be determined for each victim-perpetrator pair.

**E. BSEP.** Endogenous compound/drug interactions are mediated by the bile salt export pump (BSEP). BSEP is an ATP-dependent efflux transporter localized in the canalicular membrane of hepatocytes (Fig. 2) that transports bile salts from the hepatocytes into bile. Inhibition of BSEP by certain drugs increases accumulation of hepatotoxic bile salts within the hepatocytes, leading to cholestatic liver injury. Drugs such as cyclosporine, rifampin, glibenclamide, and bosentan are competitive inhibitors of BSEP (Pauli-Magnus et al., 2010; Russmann et al., 2010) and can cause cholestatic liver injury via this mechanism (Table 4). Genetic variations in the gene encoding for BSEP causing a reduced expression of the protein (e.g., c.1331T>C) have been shown to increase the risk for drug-induced cholestasis (Lang et al., 2007).

**F. BCRP.** In vitro studies identified multiple drugs, such as statins (e.g., atorvastatin), anti-infective drugs, and antineoplastic agents (e.g., mitoxantrone, topotecan, gefitinib, imatinib), as substrates of BCRP (Poguntke

et al., 2010; Meyer zu Schwabedissen and Kroemer, 2011; Mandery et al., 2012). Studies in Bcrp-deficient mice showed a major effect of Bcrp on plasma concentrations of sulfasalazine and topotecan (Jonker et al., 2000; Zaher et al., 2006). Oral administration of the P-gp/Bcrp inhibitor GF120918 (elacridar) to *mdr1a/1b(-/-)* mice and to P-gp-expressing mice increased systemic exposure after oral administration of topotecan sevenfold and 10-fold, respectively (Jonker et al., 2000; Kruijtzter et al., 2002). Moreover, elacridar increased the (re-)uptake of topotecan by the small intestine (Jonker et al., 2000). In a proof-of-concept study in patients with solid tumors, Kruijtzter et al. (2002) showed that elacridar increased the apparent oral bioavailability of topotecan from 40.0% without to 97.1% with elacridar (Table 3).

In humans, disposition of atorvastatin and rosuvastatin is influenced by the c.421C>A polymorphism in the *ABCG2* gene encoding BCRP (Zhang et al., 2006; Keskitalo et al., 2009a), which causes a reduced function of BCRP. Moreover, Keskitalo et al. (2009a) also detected higher plasma concentrations of fluvastatin and simvastatin lactone in individuals with the *ABCG2*c.421AA genotype compared with the c.421CC genotype. BCRP appears to affect disposition of these statins primarily during the absorption phase (Neuvonen, 2010). In contrast to the statins mentioned above, this polymorphism in the *ABCG2* gene did not influence pharmacokinetics of pravastatin, pitavastatin, and simvastatin acid (Zhang et al., 2006; Ieiri et al., 2007; Keskitalo et al., 2009a,b). On the basis of these data, it can be speculated that inhibitors or inducers of BCRP might influence disposition of certain statins (Neuvonen, 2010); the extent of the interaction might vary between the statins and between different *ABCG2* genotypes. Clearly, further work is required to clarify the role of BCRP in drug interactions with statins.

#### IV. Drug-Food Interactions

In addition to drug-drug interactions, interactions between food constituents and drugs are also of particular interest. Grapefruit juice is one of the most intensively studied dietary substances and can significantly enhance systemic drug exposure in humans by up to 14-fold (Huang et al., 2004; Won et al., 2010). The first grapefruit juice-drug interaction was serendipitously identified by Bailey et al. (1989). They investigated the interaction between ethanol and felodipine in 10 volunteers and found that felodipine bioavailability was not influenced by ethanol, but felodipine plasma concentrations greatly increased in volunteers treated with grapefruit juice used as a vehicle. Since then the effects of grapefruit juice and its constituents on drug disposition have been investigated in detail both in vitro and in vivo. Grapefruit juice is rich in a number of phytochemicals, including furanocoumarins and

TABLE 4  
Adverse drug reactions of selected drugs and associations with transporter function

In many of these examples the involvement of additional transporters and other factors (e.g., drug metabolism) needs to be considered.

Drug	Adverse Drug Reaction	Transporter	Reference
Adefovir	Nephrotoxicity	OAT1	Ho et al., 2000; Servais et al., 2006
Bosentan	Cholestatic liver injury	BSEP	Fattinger et al., 2001
Cidofovir	Nephrotoxicity	OAT1	Ho et al., 2000
Cisplatin	Nephrotoxicity	OCT2	Filipski et al., 2009; Ciarimboli et al., 2010
Cyclosporine	Cholestatic liver injury	BSEP	Byrne et al., 2002
	Nephrotoxicity	P-gp	Zolk and Fromm, 2011
Glibenclamide	Cholestatic liver injury	BSEP	Byrne et al., 2002
Irinotecan	Diarrhea	MRP2	de Jong et al., 2007
	Myelosuppression	BCRP	Cha et al., 2009
Loperamide	Respiratory depression	P-gp	Sadeque et al., 2000
Metformin	Hyperlactacidemia, lactic acidosis	Organic cation transporters	Zolk, 2012
Methotrexate	Nephrotoxicity	MRP2	Hulot et al., 2005; Vlaming et al., 2009
Mycophenolate mofetil	Leucopenia, anemia, thrombocytopenia, diarrhea, nausea, vomiting, infection	OATP1B1	Michelon et al., 2010
Rifampin	Cholestatic liver injury	BSEP	Byrne et al., 2002
Simvastatin	Myopathy	OATP1B1	Link et al., 2008; Voora et al., 2009; Brunham et al., 2012
Tacrolimus	Nephrotoxicity	P-gp	Zolk and Fromm, 2011
Tenofovir	Nephrotoxicity	OAT1	Ray et al., 2006
Troglitazone	Cholestatic liver injury	BSEP	Funk et al., 2001

flavonoids, with naringin being the most abundant one (De Castro et al., 2006). Many studies have demonstrated that grapefruit juice-induced mechanism-based inhibition of intestinal CYP3A4 by furanocoumarins is the underlying mechanism of multiple interactions (Won et al., 2010).

More recently, inhibition of intestinal uptake and efflux transporters has intensively been studied as a potential mechanism of drug-food interactions (for review, see Greenblatt, 2009; Bailey, 2010; Won et al., 2010). It has been demonstrated in vitro that the OATP1A2-mediated uptake of fexofenadine is inhibited by grapefruit juice (Dresser et al., 2002). This juice at concentrations from 0.5 to 5% caused a concentration-dependent inhibition that ranged from 50 to 90% decrease. The  $IC_{50}$  of naringin for the inhibition of OATP1A2-mediated fexofenadine uptake was 3.6  $\mu$ M, which is a concentration much lower than that causing equivalent inhibition of P-gp and lower than generally found in grapefruit juice (Bailey et al., 2007). Furthermore, it has been demonstrated that naringin and its aglycone naringenin also inhibited OATP1B1-mediated uptake of DHEAS (Wang et al., 2005).

A number of clinical studies in humans reported a decrease in plasma concentrations of OATP substrates (e.g., fexofenadine, talinolol, etoposide, montelukast, aliskiren) when coadministered with grapefruit juice (Won et al., 2010). One of the first OATP substrates reported to interact with grapefruit juice was fexofenadine (Dresser et al., 2002), with AUC ratios between 0.37 and 0.67 and lower AUC values associated with higher intake of grapefruit juice. Interestingly and unlike its effect on CYP3A4, the observed inhibition of OATP-mediated drug uptake seems to be an effect with a short duration, suggesting that grapefruit juice may not destroy transport proteins via mechanism-based

inhibition (Glaeser et al., 2007). An interesting study combining in vitro and in vivo data has been published recently analyzing the effect of grapefruit juice on the pharmacokinetics of the selective renin inhibitor aliskiren (Rebello et al., 2012). In this study, the authors demonstrated that coadministration of a single dose of aliskiren with grapefruit juice decreased  $C_{max}$  and AUC of aliskiren. It is interesting that by use of HEK293 cells recombinantly overexpressing OATP1A2 or OATP2B1, both transporters reported to be expressed in enterocytes, they found that OATP2B1-mediated aliskiren uptake was unaffected by naringenin but inhibited in HEK-OATP1A2 cells, with an  $IC_{50}$  value of 75.5  $\mu$ M. These results suggest that grapefruit juice decreases exposure of aliskiren via inhibition of OATP1A2-mediated uptake.

A second transporter studied intensively regarding its transport inhibition by grapefruit juice is P-gp. Several publications have demonstrated in vitro an inhibition of P-gp transport activity by grapefruit juice, grapefruit juice constituents, and extracts of juice (Eagling et al., 1999; Ohnishi et al., 2000; Paine et al., 2008). By use of Caco-2 cells, it has been demonstrated that grapefruit juice inhibits the basal-to-apical transport of colchicines (Dahan and Amidon, 2009) or that grapefruit juice constituents inhibits P-gp-mediated efflux of vinblastine (Ohnishi et al., 2000).

Despite the fact that the in vitro data suggest significant P-gp-mediated transport inhibition by grapefruit juice, definitive evidence supporting clinically relevant in vivo inhibition of P-gp is limited. Studies using biopsy samples have demonstrated that the P-gp mRNA and protein amount are unchanged after grapefruit juice ingestion, which is similar to the effect of grapefruit juice on OATPs, suggesting that this inhibition is also short lived (Lown et al., 1997; Glaeser

et al., 2007). Digoxin transport has been used intensively as P-gp substrate *in vitro*, and grapefruit juice reduces digoxin transport in cell culture models. Nevertheless, grapefruit juice has only a minor effect on the pharmacokinetics of digoxin as shown in two studies (Becquemont et al., 2001; Parker et al., 2003), suggesting that the overall effect of grapefruit juice on P-gp-mediated drug transport (at least for digoxin) is limited. Taken together P-gp inhibition by grapefruit juice appears to be of limited clinical significance. Most drugs transported by P-gp are also substrates of CYP3A4, thereby making it difficult to assign an observed effect to the transporter. Other nonmetabolized P-gp substrates (e.g., fexofenadine) are also substrates for members of the OATP family.

Orange juice contains minor amounts of furanocoumarins and has little CYP3A4 inhibitory effect (Takanaga et al., 2000; Won et al., 2010). It has been demonstrated that orange juice reduces the AUC of celiprolol (Lilja et al., 2004), atenolol (Lilja et al., 2005), fexofenadine (Dresser et al., 2002), ciprofloxacin (Neuhofel et al., 2002), and levofloxacin (Wallace et al., 2003). Because at least some of these drugs (e.g., fexofenadine, celiprolol) have been identified as substrates of OATPs expressed in the intestine, uptake inhibition of these transporters may be the cause for these interactions. By use of hesperidin, a major component of orange juice, as a possible inhibitor of OATP1A2-mediated fexofenadine uptake *in vitro*, an  $IC_{50}$  of  $2.7 \mu\text{M}$  was detected (Bailey et al., 2007). By use of rats, it could be demonstrated *in vivo* that the AUC of celiprolol was decreased when hesperidin or orange juice was administered simultaneously into the duodenum (Uesawa and Mohri, 2008). In a study investigating the effects of orange juice on the pharmacokinetics of pravastatin in rats and healthy volunteers, Koitabashi et al. (2006) demonstrated that the AUC of pravastatin was significantly increased in rats and humans treated with orange juice compared with the controls treated with water. The mechanism underlying this interaction remains to be elucidated.

Apple juice coadministration also resulted in reduced plasma concentrations of some drugs [e.g., atenolol, celiprolol, ciprofloxacin, fexofenadine (Bailey, 2010)]. For example, apple juice caused a reduction of fexofenadine AUC of 70% after administration of a single oral dose of fexofenadine (Dresser et al., 2002). By using HeLa cells expressing OATP1A2 to investigate the uptake of fexofenadine in the presence and absence of apple juice, it was demonstrated that the highest tested concentration of juice (5% v/v) inhibited transport by 85%. These results were expanded in an *in vitro* study analyzing the influence of the flavonoids quercetin (present in apples), apigenin, and kaempferol on OATP2B1- and OATP1A2-mediated fexofenadine and bromosulfophthalein uptake. Quercetin inhibited OATP1A2-mediated fexofenadine uptake with an  $IC_{50}$  value of  $13 \mu\text{M}$  and OATP1A2- and

OATP2B1-mediated bromosulfophthalein uptake with  $K_i$  values of 22 and  $8.7 \mu\text{M}$ , respectively. Tapaninen et al. (2011) investigated the effects of orange and apple juice on the pharmacokinetics and pharmacodynamics of the OATP2B1 substrate aliskiren. In a randomized crossover study with 12 healthy volunteers, it was demonstrated that aliskiren AUCs were reduced by orange juice and apple juice by 62 and 63%, respectively, whereas the plasma renin activity was 87 and 67% higher during the orange juice and apple juice phase than during the control phase (Tapaninen et al., 2011).

Clinical studies on other fruit-drug interactions due to the inhibition or induction of transporters are largely missing. Nevertheless, *in vitro* studies have demonstrated that tangerine, ginger, mango, or guava could also inhibit P-gp- or OATP-mediated transport (for review, see Rodriguez-Fragoso et al., 2011).

Taken together, fruit juices affect disposition of OATP substrates. However, further studies are needed to optimize our knowledge on uptake transporter expression and localization in the small intestine as well as on specific ingredients of juices (e.g., in apple juice) causing clinically observed interactions.

## V. Induction of Uptake and Efflux Transporters

There is pronounced interindividual variability in transporter protein tissue expression (Tirona, 2011). Human drug transporters are regulated by several ligand-activated nuclear receptors such as pregnane X receptor, constitutive androstane receptor, farnesoid X receptor, and vitamin D receptor (Tirona, 2011). The number of clinically relevant drug-drug interactions, which are attributable to induction of transporter proteins, is relatively small in comparison with the described drug-drug interactions due to transporter inhibition. Most clinical studies report the impact of PXR agonists such as rifampin and St. John's wort on disposition of P-gp substrates (Table 3).

Greiner et al. (1999) reported the interaction between the P-gp substrate digoxin and the antibiotic rifampin in a study in healthy volunteers (Table 3). Rifampin treatment reduced oral bioavailability of digoxin from 58 to 30%. Duodenal biopsies revealed that P-gp expression in the small intestine increased 3.5-fold during rifampin treatment. Moreover, AUC after oral administration of digoxin was negatively correlated with intestinal P-gp expression, indicating an important role of P-gp for this drug-drug interaction. Rifampin was also shown to reduce bioavailability of the  $\beta$ -blocker talinolol in humans and intestinal P-gp expression correlated with systemic clearance of talinolol [(Westphal et al., 2000) Table 3]. Induction of intestinal P-gp is very likely also involved in the pronounced reduction of carvedilol plasma concentrations during treatment with rifampin (Giessmann et al., 2004b). St. John's wort has also been shown to

induce intestinal P-gp expression in humans (Dürr et al., 2000; Schwarz et al., 2007), and St. John's wort-mediated induction of P-gp is a major mechanism underlying the interactions with digoxin, talinolol, and fexofenadine [Table 3 (Johne et al., 1999; Dresser et al., 2003; Schwarz et al., 2007)].

Rifampin leads also to an induction of intestinal MRP2 in humans (Fromm et al., 2000; Giessmann et al., 2004b). Induction of intestinal and/or hepatic MRP2 has been implicated to play a role in the interactions observed clinically between rifampin and morphine, mycophenolate mofetil, ezetimibe, and carvedilol (Fromm et al., 1997; Giessmann et al., 2004b; Oswald et al., 2006). Carbamazepine also increased talinolol elimination in humans, most likely by induction of P-gp and MRP2 (Giessmann et al., 2004a). Cho et al. (2011) reported an induction of *SLC22A1* mRNA encoding the uptake transporter OCT1 by rifampin in peripheral blood cells and enhanced glucose-lowering effects of metformin during rifampin administration. The exact molecular mechanisms underlying these observations, in particular the effect of rifampin on hepatic OCT1 expression and metformin uptake, require further studies.

## VI. Genotype-Dependent Drug-Drug Interactions

Genetically determined differences in function of drug metabolizing enzymes have been recognized as a determinant for the extent of drug-drug interactions for many years (e.g., Brosen et al., 1993; Caraco et al., 1996). Generally, individuals with the high activity variants within genes encoding for drug-metabolizing enzymes or transporters are expected to be more sensitive regarding inhibition compared with individuals with low activity variants.

There are several examples of genotype-dependent, transporter-mediated drug-drug interactions in the literature: Wang et al. (2008) investigated in humans polymorphic OCT2 variants and the effect of cimetidine on metformin renal clearance. Individuals homozygous for the *SLC22A2c.808G>T* mutation showed only a small 12.5% decrease in metformin renal clearance when cimetidine was coadministered, whereas the respective values were 26.0 and 42.4% for the GT and GG genotype groups, respectively (Wang et al., 2008). These data indicate that individuals with the GG genotype are considerably more sensitive to cimetidine compared with subjects with the TT genotype. This finding is in agreement with in vitro data that metformin uptake into HEK cells expressing wild-type OCT2 is considerably more sensitive to inhibition by cimetidine compared with metformin uptake mediated by the mutant protein (Zolk et al., 2009).

A frequently investigated and clinically relevant polymorphism in the *SLCO1B1* gene encoding for OATP1B1 is *SLCO1B1c.521T>C* (OATP1B1\*5), with the C variant

showing reduced transporter activity. It was shown by Kajosaari et al. (2005) that the CYP3A4 and OATP1B1 inhibitor cyclosporine increased the repaglinide AUC significantly more in subjects with the TT genotype compared with the TC group. Similarly, single dose rifampin elevated atorvastatin plasma concentrations depending on *SLCO1B1* genotype with 8-, 5-, and 3-fold increases for the TT, TC, and CC groups, respectively (He et al., 2009). *SLCO1B1* genotype-dependent interactions were also observed between gemfibrozil/repaglinide and atorvastatin/repaglinide (Kalliokoski et al., 2008).

## VII. Transporter-Mediated Drug-Drug Interactions in SPCs

There is increasingly more information on the involvement of transporters in drug disposition and on transporter-mediated drug-drug interactions within the summaries of product characteristics (SPCs; see Supplemental Table 1). However, even recent updates of SPCs of "older" drugs (e.g., digoxin, metformin, simvastatin) appear to contain no or only little information on specific transporters and transporter-mediated drug-drug interactions compared with SPCs of more recently approved drugs (Supplemental Table 1). The contents of the SPCs regarding transporters and transporter-mediated drug-drug interactions vary in part considerably for the same compound between the United States and Europe (e.g., pitavastatin; Supplemental Table 1). Moreover, the extent of transporter information within Europe or within the United States is quite different even for recently approved drugs. For example, the rosuvastatin SPC contains no (United States) or very little (Germany) information on transporters, whereas the description of the interaction of sitagliptin with transporters is very detailed both in the United States and Europe (Supplemental Table 1). A problematic issue for the prescribing physician is also the fact that nomenclature for the same transporters/transporter families varies, e.g., P-glycoprotein or p-glycoprotein or P-gp or ABCB1 or OAT3 or OAT-3 or hOAT-3. Sometimes, for example, in the German version of the rosuvastatin SPC, an old nomenclature for a transporter is used (OATP-C instead of OATP1B1). In other cases, information provided in the United States and Europe for the same compound appears to be different: The concomitant systemic use of dabigatran etexilate with the strong P-gp inhibitors dronedarone, systemically administered ketoconazole, cyclosporine, itraconazole, and tacrolimus is contraindicated according to section 4.3 (contraindications) of the SPC in Germany (Pradaxa 110 mg Hartkapseln), whereas in the United States the contraindications section contains no warnings on the drugs mentioned above (SPCs accessed in July 2012). In the United States, a dose reduction of dabigatran etexilate is

recommended in patients with moderate renal impairment and coadministration of dronedarone or systemic ketoconazole. According to section 5.3. (Effect of P-gp Inducers and Inhibitors on Dabigatran Exposure) of the SPC, the administration of dabigatran with P-gp inhibitors should be avoided in patients with severe renal impairment (SPC accessed in July 2012).

### VIII. Interplay of Drug Transport and Drug Metabolism

Because drug-metabolizing enzymes are located intracellularly, the uptake of drugs across the plasma membrane is a prerequisite for their subsequent metabolism. Furthermore, export of drugs or drug metabolites also influences the kinetics of drug-metabolizing enzymes because enzyme kinetics are affected by the intracellular concentrations of drugs and/or drug metabolites. Therefore, modulation of drug uptake or efflux, e.g., by transporter-mediated drug-drug interactions or attributable to genetic variations in transporter genes, may also affect intracellular metabolism (Benet, 2009). Several comprehensive reviews have been published over the recent years on this issue (Nies et al., 2008b; Benet, 2009; Fan et al., 2010; Sissung et al., 2012).

Interestingly, distinct uptake transporters and efflux pumps (e.g., in hepatocytes) share an overlapping substrate spectrum, and the transport process can be described as a vectorial transport with the uptake of drugs across the basolateral membrane and the efflux of drugs or drug metabolites across the apical membrane. Families with such overlapping substrate spectra are uptake transporters of the OATP family and efflux pumps of the MRP family [especially the apically localized export pump MRP2 (Nies et al., 2008b)] or the OCT uptake transporters and the drug export pump P-gp or MATEs. Furthermore, most phase I (e.g., CYP3A4) and phase II (e.g., UDP-glucuronosyltransferase 1A1, UGT1A1) enzymes have a broad substrate spectrum accepting drugs transported by members of different transporter families. Therefore, uptake transporters, metabolizing enzymes, and export pumps work in concert to enable, for example, the elimination of drugs and their metabolites, and the modulation of one molecular step may result in altered drug kinetics.

Because statins have to be taken up into hepatocytes for their subsequent action as HMG-CoA-reductase inhibitors and their final metabolism and excretion, modulation of uptake kinetics affect pharmacodynamics and pharmacokinetics of this drug class. Atorvastatin, for example, is taken up by OATP1B1 [ $K_m$  value = 12  $\mu\text{M}$  (König et al., 2000a) and finally metabolized by CYP3A4 (Jacobsen et al., 2000) and UGT1A1 (Prueksaritanont et al., 2002)]. In vitro it has been demonstrated that cyclosporine inhibited OATP1B1-mediated atorvastatin transport with an  $\text{IC}_{50}$  value of 21 nM (Amundsen et al., 2010), suggesting that this

inhibition may also be relevant in vivo. This uptake inhibition may not only be relevant for increased statin plasma concentrations (with the risk of statin-induced myopathy or rhabdomyolysis) but may also affect intracellular CYP3A4- or UGT1A1-mediated metabolism of other drugs administered simultaneously.

Double- or multiple-transfected cell lines (based on polarized grown MDCKII cells) with the parallel expression of one or more uptake transporters and export pumps can be used for the analysis of vectorial transport processes (Cui et al., 2005; Kopplow et al., 2005; Nies et al., 2008a). Recently the establishment and characterization of a triple-transfected cell line expressing the uptake transporter OATP1B1, the phase II enzyme UGT1A1, and the apically localized export pump MRP2 (Fahrmayr et al., 2012) and of a quadruple-transfected cell line expressing, in addition, the phase I enzyme CYP3A4 (Fahrmayr et al., 2013) has been described. Furthermore, transporter- metabolism interplay has been investigated using organ perfusion systems or studies with Caco-2 cell monolayers (Benet et al., 2003; Pang et al., 2009). In addition, in silico models can be used to analyze the effect of the modulation of drug uptake transporter function on drug pharmacokinetics. Nevertheless, the analysis of the interplay of drug transport and drug metabolism is challenging and important in terms of deciphering the impact of change of one molecular step in drug elimination on other mechanisms and their importance for drug-drug interactions.

### IX. Conclusions and Outlook

Considerable progress has been made regarding characterization of tissue expression, localization, and quantification (e.g., mass spectrometry) of drug transporters, regulation of transporter expression, and characterization of transporter substrates and inhibitors. The new EMA Guideline on the Investigation of Drug Interactions (EMA, 2012) and the FDA (draft) guidance on drug interaction studies ([www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm292362.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm292362.pdf)) will lead to a thorough and more complete picture on the interaction of new molecular entities with drug transporters.

However, the authors of this review believe that the following issues related to transporter-mediated drug-drug interactions need particular attention during the next few years:

- Standardization of in vitro assays for transporter function to reduce between-laboratory variability;
- Search for more specific inhibitors of drug transporters for in vitro assays as well as clinical studies;
- Suitability of endogenous compounds as markers for estimation of the transporter-related interaction potential of drugs;

- Improvement of our ability to quantitatively predict the extent of transporter-mediated drug-drug interactions based on in vitro results (in vitro–in vivo extrapolations);
- Improvement of our understanding of changes in the drug metabolism–drug transport interplay during coadministration of drugs;
- Underlying mechanisms of intersubject variability in the extent of transporter-mediated drug-drug interactions after administration of the same drug combinations to different individuals.

These efforts for better understanding of general, systemic transporter-mediated drug-drug interactions should be paralleled by further research on the importance of transporter-mediated drug-drug interactions at the level of individual tissues such as blood-tissue barriers or tumors.

#### Authorship Contributions

Performed data analysis: König, Müller, Fromm.

Wrote or contributed to the writing of the manuscript: König, Müller, Fromm.

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