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REVIEW

Interaction of innovative small molecule drugs used for cancer therapy with drug transporters

K Mandery, H Glaeser and MF Fromm

Institute of Experimental and Clinical Pharmacology and Toxicology, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany

Correspondence
Martin F Fromm, Institute of Experimental and Clinical Pharmacology and Toxicology, Friedrich-Alexander-Universität Erlangen-Nürnberg, Emil Fischer Center, Fahrstraße 17, 91054 Erlangen, Germany. E-mail: martin.fromm@pharmakologie.med.uni-erlangen.de

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Multiple new small molecules such as tyrosine kinase, mammalian target of rapamycin (mTOR) and proteasome inhibitors have been approved in the last decade and are a considerable progress for cancer therapy. Drug transporters are important determinants of drug concentrations in the systemic circulation. Moreover, expression of drug transporters in blood–tissue barriers (e.g. blood–brain barrier) can limit access of small molecules to the tumour (e.g. brain tumour). Finally, transporter expression and (up)regulation in the tumour itself is known to affect local drug concentrations in the tumour tissue contributing to multidrug resistance observed for multiple anticancer agents. This review summarizes the current knowledge on: (i) small molecules as substrates of uptake and efflux transporters; (ii) the impact of transporter deficiency in knockout mouse models on plasma and tissue concentrations; (iii) small molecules as inhibitors of uptake and efflux transporters with possible consequences for drug–drug interactions and the reversal of multidrug resistance; and (iv) on clinical studies investigating the association of polymorphisms in genes encoding drug transporters with pharmacokinetics, outcome and toxicity during treatment with the small molecules.

Abbreviations

ABC, ATP-binding cassette; AUC, area under the curve; BCRP, breast cancer resistance protein; CL1, human lung adenocarcinoma cell line; C_{min}, minimum or 'trough' concentration; CEM, human leukaemic lymphoblast cell line; CML, chronic myeloid leukaemia; CYP, cytochrome P450; $E_2$17βG, estradiole-17β-glucuronide; FDA, US Food and Drug Administration; GI, gastrointestinal; GIST, gastrointestinal stromal tumour; HEK293, human embryonic kidney cell line; HL60, human myelomonocytic cell line; HMG-CoA, 3-hydroxy-3-methyl-glutaryl-CoA reductase; HSC, haematopoietic stem cell; K562, human erythromyeloblastoid leukaemia cell line; KCL-22, chronic myelogenous leukaemia cell line; K_i, inhibition constant; LLC-PK1, pig kidney epithelial cell line; MATE, multidrug and toxin extrusion protein; MCF7, human breast adenocarcinoma cell line; MDCKII, Madin-Darby canine kidney cell line; MDR1, multidrug resistance protein 1; MPP^+, 1-methyl-4-phenylpyridinium; MRP, multidrug resistance protein; mTOR, mammalian target of rapamycin; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; OCT, organic cation transporter; PC-6, human small cell lung cancer cell line; Saos2, human osteosarcoma cell line; SLCO, solute carrier gene family encoding for OATPs

Introduction

The development of new small molecules such as tyrosine kinase, mammalian target of rapamycin (mTOR) and proteasome inhibitors is a significant progress for cancer therapy. In order to achieve desired therapeutic effects, these small molecules must reach sufficient concentrations within the target cells (tumour cells, endothelial cells of tumour vessels) to

Table 1

Metabolism and excretion of small molecules used for cancer treatment. All data are derived from the US Food and Drug Administration drug labels and the German summary of product characteristics ('Fachinformation')

Compound	Bioavailability (%)	Metabolism Major	Additional	Elimination (% of radioactivity) In Urine	In faeces	Unchanged	Brand name
Dasatinib		CYP3A4	UGT	4	85	0.1 (in urine), 19 (in faeces)	Sprycel®
Erlotinib	59	CYP3A4	CYP1A2	8	83	0.3 (in urine), 1 (in faeces)	Tarceva®
Gefitinib	59	CYP3A4, CYP2D6		<4	86		Iressa®
Imatinib	98	CYP3A4	CYP1A2, CYP2D6, CYP2C9, CYP2C19	13	68	5 (in urine), 20 (in faeces)	Glivec®
Lapatinib		CYP3A4, CYP3A5	CYP2C19, CYP2C8	<2		27 (in faeces)	Tykerb®
Nilotinib	30	CYP3A4	CYP2C8		94	69	Tasigna®
Pazopanib		CYP3A4	CYP1A2, CYP2C8	<4			Votrient®
Sorafenib	38–49 (relative)	CYP3A4	UGT1A9	19	77	51 (in faeces)	Nexavar®
Sunitinib		CYP3A4		16	61		Sutent®
Everolimus		CYP3A4		5	80	0	Afinitor®
Temsirolimus		CYP3A4		4.6	78		Torisel®
Bortezomib		CYP3A4, CYP2C19, CYP1A2	CYP2D6, CYP2C9	NC	NC	NC	Velcade®

NC, not characterized in humans.

block intracellular signal transduction pathways (Krause and Van Etten, 2005).

Most new small molecules are substrates of the major drug metabolizing enzyme cytochrome P450 3A4 (CYP3A4), which is expressed in small intestine and liver (Table 1, Hartmann *et al.*, 2009; van Erp *et al.*, 2009b; Duckett and Cameron, 2010). In addition to drug metabolizing enzymes, drug transporters are now well-recognized determinants of drug disposition and effects (Ho and Kim, 2005; Funk, 2008; Zolk and Fromm, 2011). Transporters affect drug disposition and effects via different mechanisms. First, due to their expression in the small intestine, liver and kidney, they are important determinants for systemic plasma concentrations, as they influence the extent of drug absorption from the gastrointestinal (GI) tract, of hepatic drug metabolism and of biliary as well as of renal drug elimination (Figure 1; Ho and Kim, 2005; Funk, 2008). Second, drug transporters affect drug penetration into certain tissues (e.g. brain) due to their expression in blood–tissue barriers (e.g. blood–brain barrier). Third, drug transporters are expressed in tumour cells and are considered as important determinants of drug concentrations at the site of action of these drugs. One well-known example for the last mentioned mechanism is the overexpression of the *ABCB1* [multidrug resistance 1 (*MDR1*)] gene product P-glycoprotein in tumour cells as one reason for the development of resistance against certain anticancer agents. Finally, concomitant administration of two or more drugs can lead to transporter-mediated drug–drug interactions via induction or inhibition of drug transporters (Shitara *et al.*, 2005; Müller and Fromm, 2011). For example, concomitantly administered drugs used for treatment of non-tumour diseases (e.g. infections by rifampin or macrolides, depression by St John's wort, epilepsy by phenytoin or carbamazepine) can influence transporter expression or function (Ho and Kim, 2005), and therefore disposition of the transporter substrate such as small molecules used for cancer treatment.

This review focuses on the interaction of currently approved major small molecule drugs with drug transporters. Particular attention is given to *in vitro* data on small molecules as substrates and inhibitors of drug transporters as well as on clinical studies linking transporter expression or function (e.g. determined by genetic polymorphisms) with treatment outcome.

Overview on major drug transporters

Functionally, drug transporters can be categorized into two groups. The first group mediates uptake of drugs into the cells, the second group transports its substrates from the intracellular compartment out of the cells (Figure 1). The major uptake transporters are organic anion transporting polypeptide (OATP) family members [e.g. protein name: OATP1B1, respective gene name: *SLCO1B1*; OATP1B3, *SLCO1B3*; OATP2B1, *SLCO2B1*; solute carrier gene family encoding for OATPs (*SLCO*)], organic anion transporters (OATs; e.g. *SLC22A6*) and the organic cation transporter 1 (OCT1; *SLC22A1*), which are localized in the basolateral membrane of hepatocytes (Figure 1) and mediate drug uptake from the portal venous blood into the hepatocytes (König, 2011; Niemi *et al.*, 2011; Nies *et al.*, 2011). OCT2 (*SLC22A2*) is an uptake transporter localized in the basolateral membrane

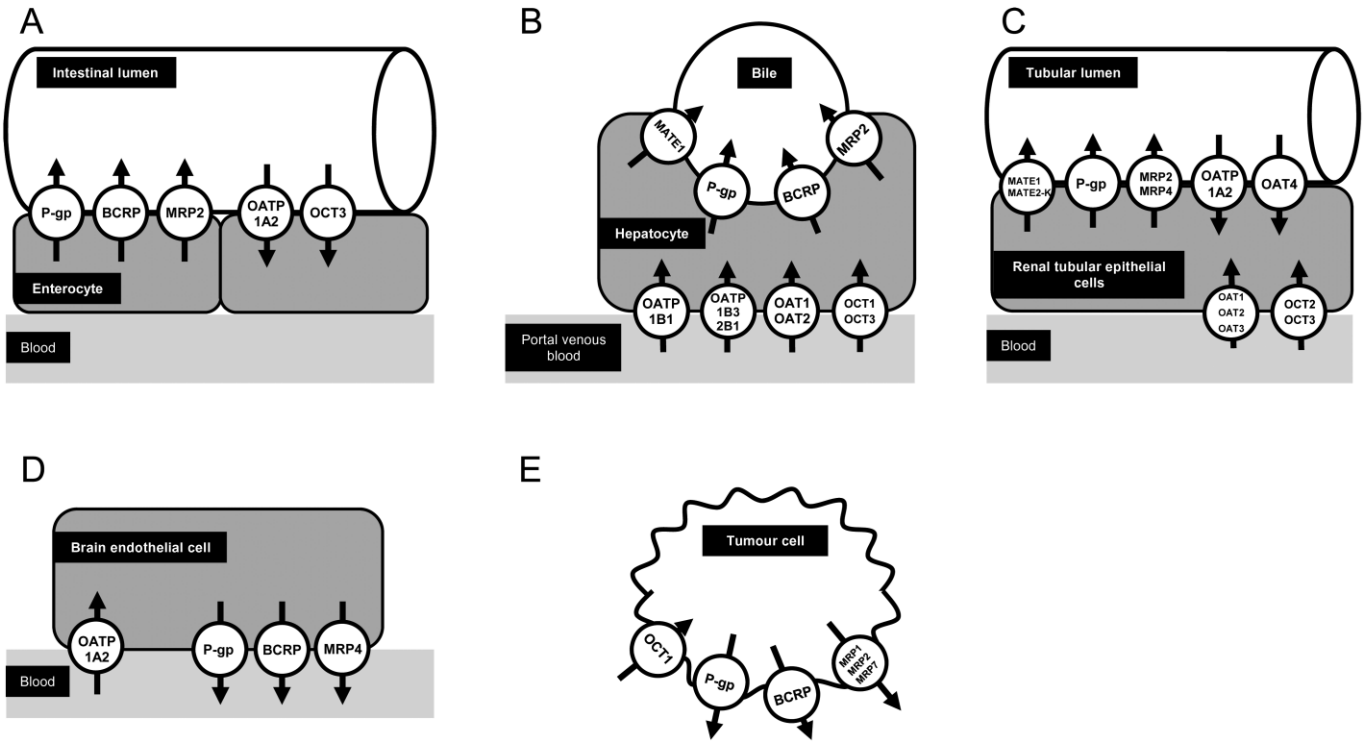

Figure 1

Tissue expression of selected drug transporters, which are involved in disposition or effects of small molecules used for cancer treatment. (A) Enterocyte. (B) Hepatocyte. (C) Renal tubular epithelial cell. (D) Brain endothelial cell. (E) Tumour cell. P-gp, P-glycoprotein.

of renal proximal tubular cells mediating the first step of renal excretion of certain drugs into urine [Figure 1 (Nies *et al.*, 2011)].

ATP-binding cassette (ABC) transporters are a group of the efflux transporter family. P-glycoprotein (gene name: *ABCB1*), breast cancer resistance protein (protein name: BCRP, gene name: *ABCG2*) and multidrug resistance protein 2 (MRP2; *ABCC2*) are localized in the apical (luminal) membrane of enterocytes, the canalicular membrane of hepatocytes and the apical membrane of renal proximal tubular cells thereby reducing drug absorption from the GI tract and mediating drug efflux into bile and urine respectively (Fromm, 2004; Keppler, 2011; zu Schwabedissen and Kroemer, 2011). Efflux transporters for cationic compounds in the liver and kidney are multidrug and toxin extrusion protein 1 (MATE1; *SLC47A1*) and 2-K, [MATE2-K; *SLC47A2*; Figure 1 (Minematsu and Giacomini, 2011; Yonezawa and Inui, 2011)].

Expression of drug transporters in tumour cells

The expression and localization of the above mentioned drug transporters in healthy tissues are well characterized. The expression and regulation of drug transporters in tumours is with some exceptions (e.g. P-glycoprotein) much less well studied. It should be considered that changes in expression levels occur during the course of the tumour disease *per se*. Moreover, treatment of the tumour (e.g. by drugs, radiotherapy) is likely to have an effect on certain transporters.

For example, the tyrosine kinase inhibitor imatinib is a substrate of OCT1, BCRP and P-glycoprotein. Mononuclear cells of patients with chronic myeloid leukaemia (CML) express these three transporters and clinical studies showed an association between OCT1 tumour cell expression or function and antitumour effects of imatinib in patients with CML (for review see Eechoute *et al.*, 2011b).

Individual small molecules and drug transporters

The subsequent paragraphs on the individual small molecules highlight the most relevant, known interactions of these compounds with drug transporters. The following sections are structured into a presentation of the interaction of small molecule kinase inhibitors (in alphabetical order) with drug transporters, followed by sections on the mTOR inhibitors everolimus and temsirolimus and the proteasome inhibitor bortezomib. An overview of the pharmacokinetic properties of the small molecules is given in Table 1. Tables 2 and 3 summarize the available information on small molecules as substrates and inhibitors of drug transporters respectively. The impact of polymorphisms in genes encoding for drug transporters on pharmacokinetics and effects of the small molecules are summarized in Table 4. All chapters on

Table 2

Overview of small molecules used for cancer therapy as substrates of drug transporters

Drug	Substrate of transporter	*In vitro*	Animal models
Dasatinib	P-glycoprotein (*ABCB1*)	CCRF-CEM cells (Hiwase *et al.*, 2008), K562 cells (Hiwase *et al.*, 2008; Hegedus *et al.*, 2009; Haouala *et al.*, 2010), MDCKII cells (Chen *et al.*, 2009; Lagas *et al.*, 2009)	*Abcb1a/1b*(–/–) mice (Lagas *et al.*, 2009), *Abcb1a/1b*(–/–) *Abcg2*(–/–) mice (Chen *et al.*, 2009; Lagas *et al.*, 2009)
	BCRP (*ABCG2*)	K562 cells (Hiwase *et al.*, 2008; Hegedus *et al.*, 2009), MDCKII cells (Chen *et al.*, 2009; Lagas *et al.*, 2009), murine fibroblast cell line MEF3.8 (Hiwase *et al.*, 2008)	*Abcb1a/1b*(–/–) *Abcg2*(–/–) mice (Chen *et al.*, 2009; Lagas *et al.*, 2009)
Erlotinib	OAT3 (*SLC22A8*)	HEK293 cells (Elmeliegy *et al.*, 2011)	
	OCT2 (*SLC22A2*)	HEK293 cells (Elmeliegy *et al.*, 2011)	
	P-glycoprotein (*ABCB1*)	LLC-PK1 cells (Marchetti *et al.*, 2008; Kodaira *et al.*, 2010), MDCKII cells (Marchetti *et al.*, 2008)	*Abcb1a/1b*(–/–) mice (Kodaira *et al.*, 2010), *Abcb1a/1b*(–/–) *Abcg2*(–/–) mice (Marchetti *et al.*, 2008; de Vries *et al.*, 2010; Kodaira *et al.*, 2010)
	BCRP (*ABCG2*)	HEK293 cells (Li *et al.*, 2007), MDCKII cells (Marchetti *et al.*, 2008; Kodaira *et al.*, 2010), Saos2 cells (Elmeliegy *et al.*, 2011)	*Abcg2*(–/–) mice (Kodaira *et al.*, 2010; Elmeliegy *et al.*, 2011), *Abcb1a/1b*(–/–) *Abcg2*(–/–) mice (Marchetti *et al.*, 2008; de Vries *et al.*, 2010; Kodaira *et al.*, 2010; Elmeliegy *et al.*, 2011)
Gefitinib	P-glycoprotein (*ABCB1*)	MDCKII cells (Agarwal *et al.*, 2010)	*Abcb1a/1b*(–/–) *Abcg2*(–/–) mice (Kawamura *et al.*, 2009; Agarwal *et al.*, 2010)
	BCRP (*ABCG2*)	HEK293 cells (Li *et al.*, 2007), MDCKII cells (Agarwal *et al.*, 2010)	*Abcb1a/1b*(–/–) *Abcg2*(–/–) mice (Kawamura *et al.*, 2009; Agarwal *et al.*, 2010)
Imatinib	OATP1A2 (*SLC21A3*)	HeLa cells (Eechoute *et al.*, 2011a), *Xenopus laevis* oocytes (Hu *et al.*, 2008; Yamakawa *et al.*, 2011; Eechoute *et al.*, 2011a)	
	OATP1B3 (*SLC21A8*)	*Xenopus laevis* oocytes (Hu *et al.*, 2008)	
	OCT1 (*SLC22A1*)	CEM cells (Thomas *et al.*, 2004), CML cells (White *et al.*, 2006), HEK293 cells (Hu *et al.*, 2008), CML cells (Wang *et al.*, 2008)	
	OCTN2 (*SLC22A5*)	HEK293 cells (Hu *et al.*, 2008)	
	P-glycoprotein (*ABCB1*)	K562 cells (Mahon *et al.*, 2003), LLC-PK1 cells (Hu *et al.*, 2008), MDCKII cells (Dai *et al.*, 2003; Thomas *et al.*, 2004)	*Abcb1a/1b*(–/–) mice (Dai *et al.*, 2003; Zhou *et al.*, 2009), *Abcb1a/1b*(–/–) *Abcg2*(–/–) mice (Zhou *et al.*, 2009)
	MRP4 (*ABCC4*)	Saos2 cells (Hu *et al.*, 2008)	
	BCRP (*ABCG2*)	HEK293 cells (Burger *et al.*, 2004), MCF7 cells (Burger *et al.*, 2004), MDCKII cells (Breedveld *et al.*, 2005), Saos2 cells (Hu *et al.*, 2008)	*Abcg2*(–/–) mice (Zhou *et al.*, 2009), *Abcb1a/1b*(–/–) *Abcg2*(–/–) mice (Zhou *et al.*, 2009)
Lapatinib	P-glycoprotein (*ABCB1*)	MDCKII cells (Polli *et al.*, 2008)	*Abcb1a/1b*(–/–) mice (Polli *et al.*, 2009), *Abcb1a/1b*(–/–) *Abcg2*(–/–) mice (Polli *et al.*, 2009)
	BCRP (*ABCG2*)	MDCKII cells (Polli *et al.*, 2008)	*Abcb1a/1b*(–/–) *Abcg2*(–/–) mice (Polli *et al.*, 2009)
Nilotinib	P-glycoprotein (*ABCB1*)	K562 cells (Mahon *et al.*, 2008)	
	BCRP (*ABCG2*)	K562 cells (Hegedus *et al.*, 2009)	
Pazopanib	P-glycoprotein (*ABCB1*)	(FDA, 2010b)	
	BCRP (*ABCG2*)	(FDA, 2010b)	

Table 2

Continued

Drug	Substrate of transporter	*In vitro*	Animal models
Sorafenib	P-glycoprotein (*ABCB1*)	Human epithelial colorectal adenocarcinoma cells (Caco-2, Gnoth *et al.*, 2010), K562 cells (Haouala *et al.*, 2010), LLC-PK1 cells (Hu *et al.*, 2009; Gnoth *et al.*, 2010), MDCKII cells (Lagas *et al.*, 2010)	*Abcb1a/1b*(–/–) mice (Hu *et al.*, 2009; Gnoth *et al.*, 2010), *Abcb1a/1b*(–/–) *Abcg2*(–/–) mice (Lagas *et al.*, 2010; Asakawa *et al.*, 2011)
	MRP2 (*ABCC2*)	LLC-PK1 cells (Shibayama *et al.*, 2011)	
	BCRP (*ABCG2*)	MDCKII cells (Lagas *et al.*, 2010; Agarwal *et al.*, 2011)	*Abcg2*(–/–) mice (Lagas *et al.*, 2010; Agarwal *et al.*, 2011), *Abcb1a/1b*(–/–) *Abcg2*(–/–) mice (Lagas *et al.*, 2010; Agarwal *et al.*, 2011; Asakawa *et al.*, 2011)
Sunitinib	P-glycoprotein (*ABCB1*)	K562 cells (Haouala *et al.*, 2010), LLC-PK1 cells (Hu *et al.*, 2009), MDCKII cells (Tang *et al.*, 2011)	*Abcb1a/1b*(–/–) mice (Hu *et al.*, 2009; Tang *et al.*, 2011), *Abcb1a/1b*(–/–) *Abcg2*(–/–) mice (Tang *et al.*, 2011)
	BCRP (ABCG2)	MDCKII cellls (Tang *et al.*, 2011)	*Abcb1a/1b*(–/–) *Abcg2*(–/–) mice (Tang *et al.*, 2011)
Everolimus	P-glycoprotein (*ABCB1*)	Caco-2 cells (Crowe and Lemaire, 1998)	*Abcb1a/1b*(–/–) mice (Chu *et al.*, 2009)
Temsirolimus	P-glycoprotein (*ABCB1*)	Caco-2 cells (Crowe and Lemaire, 1998)	
Bortezomib	P-glycoprotein (*ABCB1*)	K562 cells (Rumpold *et al.*, 2007)	

FDA, US Food and Drug Administration.

individual drugs in this review are structured in the same way and provide information (if available) in the following, identical order: (i) small molecule drug as substrate of uptake transporters; (ii) as substrate of efflux transporters; (iii) as inhibitor of uptake transporters; (iv) as inhibitor of efflux transporters; and (v) pharmacogenomic data from clinical studies in humans.

All compounds discussed in this review are extensively metabolized by CYP3A4 (van Erp *et al.*, 2009b; Hartmann *et al.*, 2009; Duckett and Cameron, 2010). It should be noted that multiple drug–drug-interactions are reported between small molecules and the CYP3A4 and P-glycoprotein inducer rifampicin or the CYP3A4 and P-glycoprotein inhibitor ketoconazole. However, the contribution of transporters such as BCRP and P-glycoprotein to induction or inhibition of CYP3A4 for these drug–drug interactions is still not completely understood.

Dasatinib

In humans, after a single oral dose of radiolabelled dasatinib, 85% of radioactivity was recovered in faeces and 4% in urine (Table 1; Brave *et al.*, 2008). Coadministration of dasatinib with the CYP3A4 inducer rifampin decreased the dasatinib area under the curve (AUC) by ~82%, and coadministration with the CYP3A4 inhibitor ketoconazole increased the dasatinib AUC fivefold (Brave *et al.*, 2008).

OCT1 does not play a significant role for dasatinib uptake (Giannoudis *et al.*, 2008; Hiwase *et al.*, 2008). *In vitro* data indicate that dasatinib is a substrate of the efflux transporters BCRP and P-glycoprotein [Table 2 (Hiwase *et al.*, 2008; Chen *et al.*, 2009; Hegedus *et al.*, 2009; Lagas *et al.*, 2009; Haouala *et al.*, 2010)]. Data from P-glycoprotein- and Bcrp-deficient mice indicate that P-glycoprotein, but not Bcrp, limits dasatinib absorption after oral drug administration [Table 2 (Lagas *et al.*, 2009)]. Moreover, dasatinib brain concentrations were considerably higher in P-glycoprotein-deficient *Abcb1a/1b* knockout mice, but not in Bcrp-deficient mice compared with wild-type mice (Chen *et al.*, 2009; Lagas *et al.*, 2009). Interestingly, *Abcb1a/1b Abcg2* knockout mice accumulated considerably more dasatinib in the brain compared with *Abcb1a/1b* knockout mice, indicating that Bcrp can partly take over P-glycoprotein function in the absence of P-glycoprotein (Chen *et al.*, 2009; Lagas *et al.*, 2009).

The inhibition of the organic cation transporters OCT1, OCT2, OCT3, MATE1 and MATE2-K by dasatinib in relation to the estimated portal venous and systemic plasma concentrations was relatively poor (Minematsu and Giacomini, 2011).

Erlotinib

In vitro experiments showed that erlotinib and its metabolite OSI-420 are substrates of the uptake transporters OAT3 and OCT2 (Elmeliegy *et al.*, 2011). *ABCG2*-transfected cells exhibited lower intracellular accumulation of erlotinib than cells lacking *ABCG2*, indicating that erlotinib is a substrate of

Table 3

Overview of small molecules used for cancer therapy as inhibitors of drug transporters

Drug	Inhibition of transporter	Substrate	*In vitro*/animal model
Dasatinib	P-glycoprotein (*ABCB1*)	Calcein-AM	K562 cells (Hegedus *et al.*, 2009)
	BCRP (*ABCG2*)	Hoechst 33342	K562 cells (Hegedus *et al.*, 2009)
Erlotinib	OCT1 (*SLC22A1*)	Metformin (IC_{50} = 0.356 μM)	HEK293 cells (Minematsu and Giacomini, 2011)
	MATE2-K (*SLC47A2*)	Metformin (IC_{50} = 3.45 μM)	HEK293 cells (Minematsu and Giacomini, 2011)
	P-glycoprotein (*ABCB1*)	Vincristine (IC_{50} = 2 μM)	K562 cells (Noguchi *et al.*, 2009)
	MRP7 (*ABCC10*)	Paclitaxel	HEK293 cells (Kuang *et al.*, 2010)
	BCRP (*ABCG2*)	$E_2$17βG, methotrexate, mitoxantrone	HEK293 (Shi *et al.*, 2007), K562 cells (Noguchi *et al.*, 2009)
Gefitinib	OCT1 (*SLC22A1*)	MPP^+	HEK293 cells (Galetti *et al.*, 2010)
	OCT2 (*SLC22A2*)	MPP^+	HEK293 cells (Galetti *et al.*, 2010)
	MATE2-K (*SLC47A2*)	Metformin (IC_{50} = 0.194 μM)	HEK293 cells (Minematsu and Giacomini, 2011)
	P-glycoprotein (*ABCB1*)	Calcein-AM, docetaxel, doxorubicin, paclitaxel, rhodamine-123, topotecan	CL1 cells (Yang *et al.*, 2005), LLC-PK1 cells (Leggas *et al.*, 2006), MCF7 cells (Kitazaki *et al.*, 2005; Yang *et al.*, 2005), human small cell lung cancer cell line PC-6 (Kitazaki *et al.*, 2005)
	BCRP (*ABCG2*)	Hoechst 33342, estrone-3-sulfate (IC_{50} = 1.0 μM), mitoxantrone, topotecan (K_i = 1.0 μM)	CL1 cells (Yang *et al.*, 2005), HL60 cells (Ozvegy-Laczka *et al.*, 2004), K562 cells (Yanase *et al.*, 2004), MCF7 cells (Yang *et al.*, 2005), PC-6 cells (Nakamura *et al.*, 2005), Saos2 cells (Leggas *et al.*, 2006)
Imatinib	OCT1 (*SLC22A1*)	Metformin (IC_{50} = 1.47 μM)	HEK293 cells (Minematsu and Giacomini, 2011)
	MATE1 (*SLC47A1*)	Metformin (IC_{50} = 0.048 μM)	HEK293 cells (Minematsu and Giacomini, 2011)
	MATE2-K (*SLC47A2*)	Metformin (IC_{50} = 0.478 μM)	HEK293 cells (Minematsu and Giacomini, 2011)
	P-glycoprotein (*ABCB1*)	Calcein-AM (K_i = 18.3 μM)	LLC-PK1 cells (Hamada *et al.*, 2003)
	MRP7 (*ABCC10*)	Paclitaxel	HEK293 cells (Shen *et al.*, 2009)
	BCRP (*ABCG2*)	Mitoxantrone, SN-38, topotecan	HEK293 cells (Burger *et al.*, 2004), MCF7 cells (Burger *et al.*, 2004), Saos2 cells (Houghton *et al.*, 2004)
Lapatinib	OATP1B1 (*SLCO21A6*)	$E_2$17βG	CHO cells (Polli *et al.*, 2008; Fachinformation, 2010)
	P-glycoprotein (*ABCB1*)	Topotecan	CHO cells (Molina *et al.*, 2008)
	MRP7 (*ABCC10*)	Paclitaxel	HEK293 cells (Kuang *et al.*, 2010)
	BCRP (*ABCG2*)	$E_2$17βG, methotrexate, SN-38, topotecan	HEK293 cells (Dai *et al.*, 2008), H1975 cells (Perry *et al.*, 2010), H358 cells (Perry *et al.*, 2010), MDA-MB-231 cells (Molina *et al.*, 2008; Perry *et al.*, 2010), Susa S/R cells (Perry *et al.*, 2010)
Nilotinib	OCT1 (*SLC22A1*)	Metformin	CML cells (Davies *et al.*, 2009), HEK293 cells (Minematsu and Giacomini, 2011)
	OCT3 (*SLC22A3*)	Metformin (IC_{50} = 0.35 μM)	HEK293 cells (Minematsu and Giacomini, 2011)
	P-glycoprotein (*ABCB1*)	Calcein-AM, dasatinib, rhodamine	CML cells (Davies *et al.*, 2009; Hiwase *et al.*, 2010), HEK293 cells (Dohse *et al.*, 2010), K562 cells (Hegedus *et al.*, 2009)
	MRP7 (*ABCC10*)	Paclitaxel	HEK293 cells (Shen *et al.*, 2009)
	BCRP (*ABCG2*)	$E_2$17βG, Hoechst 33342, methotrexate (K_i = 0.69 μM), pheophorbide A	CML cells (Davies *et al.*, 2009), HEK293 cells (Tiwari *et al.*, 2009; Dohse *et al.*, 2010), HSC cells (Brendel *et al.*, 2007), K562 cells (Hegedus *et al.*, 2009)
Pazopanib	OATP1B1 (*SLC21A6*)		(FDA, 2010b; Keisner and Shah, 2011)
	P-glycoprotein (*ABCB1*)		(FDA, 2010b)
	BCRP (*ABCG2*)		(FDA, 2010b)

Table 3

Continued

Drug	Inhibition of transporter	Substrate	*In vitro*/animal model
Sorafenib	P-glycoprotein (*ABCB1*)	Calcein-AM, vinblastine	LLC-PK1 (Hu *et al.*, 2009), MDCKII cells (Agarwal *et al.*, 2011)
	MRP2 (*ABCC2*)	Docetaxel	Saos2 cells (Hu *et al.*, 2009)
	MRP4 (*ABCC4*)	PMEA	Saos2 cells (Hu *et al.*, 2009)
	BCRP (*ABCG2*)	Hoechst 33342	Saos2 cells (Hu *et al.*, 2009)
Sunitinib	P-glycoprotein (*ABCB1*)	Calcein-AM, rhodamine 123, vincristine (K_i = 7.6 μM)	HEK293 cells (Shukla *et al.*, 2009), K562 cells (Kawahara *et al.*, 2010), LLC-PK1 cells (Hu *et al.*, 2009)
	MRP2 (*ABCC2*)	Docetaxel	Saos2 cells (Hu *et al.*, 2009)
	MRP4 (*ABCC4*)	PMEA	Saos2 cells (Hu *et al.*, 2009)
	BCRP (*ABCG2*)	Estrone-3-sulfate (K_i = 0.32 μM), Hoechst 33342, methotrexate, pheophorbide A, rhodamine 123	HEK293 cells (Dai *et al.*, 2009; Shukla *et al.*, 2009), K562 cells (Kawahara *et al.*, 2010), Saos2 cells (Hu *et al.*, 2009), S1-M1-80 cells (Dai *et al.*, 2009)
Everolimus	OATP1A2 (*SLC21A3*)	Estrone-3-sulfate (IC_{50} = 4.2 μM)	Picard *et al.*, 2011
	OATP1B1 (*SLC21A6*)	Estrone-3-sulfate (IC_{50} = 4.1 μM)	Picard *et al.*, 2011
	OATP1B3 (*SLC21A8*)	Mycophenolic acid 7-O-glucuronide (IC_{50} = 4.3 μM)	Picard *et al.*, 2011
Temsirolimus	OATP1A2 (*SLC21A3*)	Estrone-3-sulfate (IC_{50} = 11.9 μM)	Picard *et al.*, 2011
	OATP1B1 (*SLC21A6*)	Estrone-3-sulfate (IC_{50} = 9.8 μM)	Picard *et al.*, 2011
	OATP1B3 (*SLC21A8*)	Mycophenolic acid 7-O-glucuronide (IC_{50} = 1.3 μM)	Picard *et al.*, 2011
	P-glycoprotein (*ABCB1*)		Fachinformation, 2011
Bortezomib	NC	NC	NC

FDA, US Food and Drug Administration; NC, not characterized in humans.

BCRP (Li *et al.*, 2007; Elmeliegy *et al.*, 2011). *In vitro*, erlotinib was transported by mouse and human P-glycoprotein and by Bcrp/BCRP (Li *et al.*, 2007; Marchetti *et al.*, 2008; Kodaira *et al.*, 2010; Elmeliegy *et al.*, 2011). No active transport of erlotinib by MRP2 was observed using Madin-Darby canine kidney cell (MDCKII)-MRP2 monolayers (Marchetti *et al.*, 2008). Several studies investigated erlotinib disposition in mice deficient for P-glycoprotein and/or Bcrp (Marchetti *et al.*, 2008; de Vries *et al.*, 2010; Kodaira *et al.*, 2010; Elmeliegy *et al.*, 2011). Marchetti *et al.* (2008) reported that calculated apparent oral bioavailability of erlotinib was significantly increased in *Abcb1a/1b Abcg2* knockout mice (60.4%) compared with wild-type mice (40.0%; $P = 0.02$). The absence of P-glycoprotein or the simultaneous absence of Bcrp and P-glycoprotein had greater effects than the absence of Bcrp alone on brain and testis concentrations of erlotinib in the knockout mouse models as reported by Kodaira *et al.* (2010) and de Vries *et al.* (2010). This is in contrast to the report by Elmeliegy *et al.* (2011), who concluded that Bcrp is the major efflux transporter preventing erlotinib penetration into mouse brain.

Erlotinib inhibits the organic cation transporters MATE2-K and OCT1 at potentially clinical relevant concentrations [Table 3 (Minematsu and Giacomini, 2011)]. *In vitro*, erlotinib reverses BCRP-mediated multidrug resistance (Shi *et al.*, 2007; Noguchi *et al.*, 2009). Modulation of P-glycoprotein-mediated drug resistance by erlotinib appears to be substrate dependent (Shi *et al.*, 2007; Noguchi *et al.*, 2009). In addition, Kuang *et al.* reported that erlotinib potently reverses MRP7-mediated multidrug resistance (Kuang *et al.*, 2010).

Thomas *et al.* (2009) reported population pharmacokinetics in erlotinib-treated patients with head and neck squamous cell carcinoma. Among other factors, the association of polymorphisms in *ABCB1*, *ABCG2* and *CYP3A5* with erlotinib clearance was investigated. Interestingly, patients with at least one *ABCG2* variant allele (c.421A) had a significant 24% decrease in erlotinib clearance, whereas no association was found with the polymorphisms in *ABCB1* and *CYP3A5* (Thomas *et al.*, 2009). In a study on determinants of erlotinib disposition and toxicity in 80 patients, Rudin *et al.* showed that a diplotype of two polymorphic loci in the *ABCG2* promoter involving –15622C>T and 1143C>T was associated with a higher erlotinib AUC (Rudin *et al.*, 2008). In contrast to the study by Thomas *et al.* (2009), in this study the *ABCG2* c.421C>A polymorphism was not associated with erlotinib disposition (Rudin *et al.*, 2008).

Table 4

Pharmacogenomics of small molecules used for cancer therapy. The influence of drug uptake and efflux transporters on pharmacokinetics (PK) and/or pharmacodynamics (PD) are shown

Drug	Transporter (gene)	Genotype/ polymorphism	Effect on PK	Effect on PD (outcome, toxicity)	Reference
Erlotinib	BCRP (*ABCG2*)	c.421C>A	Clearance reduced by 24% (head and neck squamous cell carcinoma)		(Thomas *et al.*, 2009)
		c.1143/–15622 diplotypes (CC/TT) or (TT/TT)	Higher AUC and C_{max} (non-small-cell lung cancer, head and neck cancer, and ovarian cancer)	No influence on diarrhea or skin toxicity	(Rudin *et al.*, 2008)
	P-glycoprotein (*ABCB1*)	c.2677G>T/A	No influence on pharmacokinetics (head and neck squamous cell carcinoma)		(Thomas *et al.*, 2009)
		c.3435C>T	No influence on pharmacokinetics (head and neck squamous cell carcinoma)		(Thomas *et al.*, 2009)
Gefitinib	BCRP (*ABCG2*)	c.421C>A	Trend to higher $C_{ss,\ min}$ (n.s., trough concentrations at steady state; malignant solid tumours)		(Li *et al.*, 2007)
		c.421C>A	Increased drug accumulation (ratio of trough concentrations at steady state to day 1 trough concentration; malignant solid tumours)		(Li *et al.*, 2007)
		c.421C>A		Increased risk of diarrhea (non-small-cell lung cancer)	(Cusatis *et al.*, 2006)
		c.421C>A		No influence on risk of skin toxicity (non-small-cell lung cancer)	(Cusatis *et al.*, 2006)
		c.421C>A		No effect on adverse side effects for example, diarrhea, interstitial pneumonia (non-small-cell lung cancer)	(Akasaka *et al.*, 2010)
		–15622TT		Increased risk of diarrhea (non-small-cell lung cancer)	(Lemos *et al.*, 2011)
		haplotype TT (c.1143C>T, –15622C>T)		Increased risk of higher grade diarrhea (non-small-cell lung cancer)	(Lemos *et al.*, 2011)
	P-glycoprotein (*ABCB1*)	c.3435C>T	No influence on pharmacokinetics		(Li *et al.*, 2007)
		c.3435C>T		No influence on risk of diarrhea (non-small-cell lung cancer)	(Cusatis *et al.*, 2006)
		c.3435C>T		No influence on risk of skin toxicity (non-small-cell lung cancer)	(Cusatis *et al.*, 2006)
Imatinib	OATP1A2 *(SLCO1A2)*	–361GG	Reduced imatinib clearance (CML)		(Yamakawa *et al.*, 2011)
	OATP1B3 (*SLCO1B3*)	c.334T>G	No influence on plasma trough concentrations (CML)	Higher rates of major molecular response (CML)	(Takahashi *et al.*, 2010)
		c.334T>G	Higher intracellular concentrations of imatinib in leukocytes (chronic phase CML)		(Nambu *et al.*, 2011)
		c.334T>G	Higher intracellular (leukocytes) to plasma ratio of imatinib (chronic phase CML)		(Nambu *et al.*, 2011)

Table 4

Continued

Drug	Transporter (gene)	Genotype/ polymorphism	Effect on PK	Effect on PD (outcome, toxicity)	Reference
	OCT1 (*SLC22A1*)	c.156T>C	No influence on plasma trough concentrations (CML)	No influence on major molecular response (CML)	(Takahashi *et al.*, 2010)
		c.286C>T	No change in oral imatinib clearance		(Hu *et al.*, 2008)
		c.480GG		Increased risk for imatinib resistance due to loss of response and treatment failure (CML)	(Kim *et al.*, 2009)
		c.480C>G	No influence on plasma trough concentrations (CML)	No influence on major molecular response (CML)	(Takahashi *et al.*, 2010)
		c.1022C>T	No influence on plasma trough concentrations (CML)	No influence on major molecular response (CML)	(Takahashi *et al.*, 2010)
		c.1222GG	No influence on plasma trough concentrations (CML)	Higher rates of major molecular response (CML)	(Takahashi *et al.*, 2010)
		c.1498C>A	No change in oral imatinib clearance		(Hu *et al.*, 2008)
	BCRP (*ABCG2*)	c.34GG		Decreased major and complete cytogenetic response (CML)	(Kim *et al.*, 2009)
		c.421CC		Decreased complete molecular response (CML)	(Kim *et al.*, 2009)
		c.421C>A	No influence on oral clearance (GIST)		(Gardner *et al.*, 2006)
		c.421C>A	Increased plasma trough concentrations (CML)	No influence on major molecular response (CML)	(Takahashi *et al.*, 2010)
	P-glycoprotein (*ABCB1*)	c.3435TT		Decreased overall survival (univariate analysis, CML)	(Kim *et al.*, 2009)
		c.3435C>T	No influence on the oral clearance (GIST)		(Gardner *et al.*, 2006)
		c.1236TT; c.2677TT; c.3435TT	Increased oral clearance (GIST)		(Gurney *et al.*, 2007)
		c.1236C>T		Higher major molecular response (CML)	(Dulucq *et al.*, 2008)
		c.1236C>T	Higher imatinib trough concentrations (CML)		(Dulucq *et al.*, 2008)
		c.1236TT		Increased resistance [cytogenetic resistance or relapse after major cytogenetic response (MCyR, CML)]	(Ni *et al.*, 2011)
		c.1236C>T	No influence on plasma trough concentrations (CML)	No influence on major molecular response (CML)	(Takahashi *et al.*, 2010)
		c.2677TT / TA		Higher major molecular response (CML)	(Dulucq *et al.*, 2008)
		c.2677GT		Increased resistance (cytogenetic resistance or relapse after MCyR)	(Ni *et al.*, 2011)
		c.2677G>T/A	No influence on plasma trough concentrations (CML)	No influence on major molecular response (CML)	(Takahashi *et al.*, 2010)
		c.2677AG / AT / AA		Lower resistance (cytogenetic resistance or relapse after MCyR)	(Ni *et al.*, 2011)

Table 4

Continued

Drug	Transporter (gene)	Genotype/ polymorphism	Effect on PK	Effect on PD (outcome, toxicity)	Reference
		c.3435CC		Lower resistance (cytogenetic resistance or relapse after MCyR)	(Ni *et al.*, 2011)
		c.3435C>T	No influence on plasma trough concentrations (CML)	No influence on major molecular response (CML)	(Takahashi *et al.*, 2010)
		haplotype TC or TT (c.1236C>T; c.3435C>T	Higher imatinib trough concentrations (CML)		(Dulucq *et al.*, 2008)
		c.1236C; c.2677G; c.3435C		Lower major molecular response (CML)	(Dulucq *et al.*, 2008)
	MRP2 (*ABCC2*)	–24C>T	No influence on plasma trough concentrations (CML)	No influence on major molecular response (CML)	(Takahashi *et al.*, 2010)
Sunitinib	BCRP (*ABCG2*)	c.34G>A		Trend for increased progression free survival (n.s., clear-cell metastatic renal cell carcinoma)	(van der Veldt *et al.*, 2011)
		422AA	Higher blood concentrations (renal cell carcinoma)		(Mizuno *et al.*, 2010)
		haplotype TT; –15622C>T, c.1143C>T		Increased risk for toxicity (>grade 2 CTCAE, metastatic renal cell carcinoma, GIST)	(van Erp *et al.*, 2009a)
	P-glycoprotein (*ABCB1*)	haplotype TCG (c.3435C>T; c.1236C>T; c.2677G>T)		Increased progression free survival (clear-cell metastatic renal cell carcinoma)	(van der Veldt *et al.*, 2011)
		haplotype TTT (c.1236C>T, c.2677G>T, c.3435C>T)		Increased risk for hand-foot syndrome (metastatic renal cell carcinoma, GIST)	(van Erp *et al.*, 2009a)

GIST, gastrointestinal stromal tumours.

Gefitinib

Gefitinib is not a substrate of OCT1 and OCT2, which was shown using transporter-overexpressing HEK293 cells (Galetti *et al.*, 2010). *In vitro* studies using MDCKII cells showed that human P-glycoprotein effectively transports gefitinib (Agarwal *et al.*, 2010). Gefitinib was also efficiently transported by mouse Bcrp in MDCK-Bcrp monolayers (Agarwal *et al.*, 2010). Stewart *et al.* (2004) and Nakamura *et al.* (2005) reported that gefitinib is not a substrate of human BCRP, whereas Li *et al.* (2007) detected a significantly lower gefitinib accumulation in BCRP overexpressing HEK cells at lower concentrations. *In vivo* studies in knockout mice or using P-glycoprotein/Bcrp inhibitors revealed that transport of gefitinib across the blood–brain barrier is significantly limited by P-glycoprotein and Bcrp (Kawamura *et al.*, 2009; Agarwal *et al.*, 2010). Steady-state brain-to-plasma concentration ratios were 70-fold higher in the *Abcb1a/1b*(–/–) *Abcg2*(–/–) mice than in wild-type mice (Agarwal *et al.*, 2010). Brain-to-plasma concentration ratios after oral administration of gefitinib were also significantly higher in P-glycoprotein-deficient, Bcrp expressing animals compared with wild-type animals, whereas the absence of Bcrp alone did not affect gefitinib brain-to-plasma concentration ratios (Agarwal *et al.*, 2010).

Among the organic cation transporters gefitinib inhibited the MATE2-K-mediated transport of metformin with the greatest potency (Minematsu and Giacomini, 2011). Moreover, gefitinib inhibits OCT1- and OCT2-mediated 1-methyl-4-phenylpyridinium (MPP^+) uptake (Galetti *et al.*, 2010). Kitazaki *et al.* showed that gefitinib reverses the P-glycoprotein-mediated resistance to paclitaxel and docetaxel in a dose-dependent manner, indicating that gefitinib inhibits P-glycoprotein (Kitazaki *et al.*, 2005). Moreover, gefitinib inhibited the BCRP-mediated topotecan transport in inside-out membrane vesicles of PC-6/SN2-5H cells with an inhibition constant (K_i) value of 1.0 μM (Nakamura *et al.*, 2005). In human BCRP-transfected erythromyeloblastoid leukaemia cells (K562), gefitinib inhibited the BCRP-mediated transport of estrone-3-sulfate (Yanase *et al.*, 2004). In addition, gefitinib increased the accumulation of topotecan in K562/BCRP cells (Yanase *et al.*, 2004). Yang *et al.* reported that

gefitinib reverses the resistance to paclitaxel in human lung adenocarcinoma cells (CL1/Pac) and to doxorubicin in human breast adenocarcinoma cells (MCF7/Adr) by inhibition of P-glycoprotein and to topotecan in MCF7/TPT and CL1/Tpt cells by inhibition of BCRP (Yang *et al.*, 2005). *In vivo*, gefitinib increased the oral bioavailability of irinotecan after concomitant administration in mice (Stewart *et al.*, 2004). Additionally, gefitinib coadministration further decreased the systemic clearance of topotecan in *Abcb1a/1b*(–/–) and *Abcg2*(–/–) mice, indicating that additional transporters were inhibited (Leggas *et al.*, 2006). It also increased topotecan brain penetration in a mouse model (Zhuang *et al.*, 2006). Furthermore, Ozvegy-Laczka *et al.* (Ozvegy-Laczka *et al.*, 2004) used human myelomonocytic cells (HL60/PLB) overexpressing BCRP, P-glycoprotein or MRP1 to determine mitoxantrone accumulation with and without addition of gefitinib. The tyrosine kinase inhibitor led to a significant increase in mitoxantrone accumulation in the BCRP-expressing HL60/PLB cells, whereas the effect was considerably smaller with the P-glycoprotein- and MRP1-expressing HL60/PLB cells (Ozvegy-Laczka *et al.*, 2004). Very recently, Huang *et al.* (2011) reported that nuclear translocation of the epidermal growth factor receptor by AKT-dependent phosphorylation enhances BCRP expression in gefitinib-resistant cells, thus providing insights into one potential molecular mechanism contributing to gefitinib-resistance via BCRP expression.

In humans, dose-normalized plasma concentrations following multiple doses of gefitinib were significantly higher in patients heterozygous for the *ABCG2* c.421C>A polymorphism, whereas no significant effects were observed for the *ABCB1* c.3435C>T polymorphism (Li *et al.*, 2007). In a recent study in 94 patients with non-small-cell lung cancer treated with gefitinib *ABCG2* polymorphisms were not associated with outcome (Lemos *et al.*, 2011). However, the *ABCG2* polymorphism –15622C>T and the *ABCG2* (c.1143C>T, –15622C>T) haplotype were associated with gefitinib-dependent, moderate-to-severe diarrhea (Lemos *et al.*, 2011). In another study, an association between the *ABCG2* c.421C>A polymorphism and diarrhea in patients with locally advanced or metastatic non-small-cell lung cancer treated with gefitinib was reported (Cusatis *et al.*, 2006). In contrast, Akasaka *et al.* did not find any association between *ABCG2* polymorphisms (c.376C>T, c.421C>A) and gefitinib-induced adverse events in Japanese patients with non-small-cell lung cancer (Akasaka *et al.*, 2010).

Imatinib

Among all drugs discussed in this review, there is the largest amount of data available for imatinib, which is also discussed in detail in a recent review by Eechoute *et al.*, (2011b). It was reported by Thomas *et al.* that the uptake of imatinib is mediated by OCT1, because inhibitors of OCT1 significantly decreased imatinib uptake into human leukaemic lymphoblast cells (CEM, Thomas *et al.*, 2004). In addition, the intracellular uptake and retention of imatinib was 20% higher in transfected HEK293 cells overexpressing OCT1, indicating that imatinib is only moderately transported by OCT1 (Hu *et al.*, 2008). Furthermore, Wang *et al.* showed that OCT1 transported imatinib in human chronic myelogenous leukaemia (CML) cells (KCL-22) overexpressing OCT1 (Wang *et al.*, 2008). *Ex vivo*, the addition of prazosin, a potent inhibitor of OCT1, reduced the intracellular uptake of imatinib into mononuclear cells (White *et al.*, 2006). OCT2 and OCT3 did not transport imatinib *in vitro* (Thomas *et al.*, 2004). In contrast, significantly higher uptake rates for imatinib were found in cells transfected with OATP1A2 (*Xenopus laevis* oocytes), OATP1B3 (*Xenopus laevis* oocytes) and OCTN2 (HEK293 cells; Hu *et al.*, 2008). Imatinib was not transported by OATP1B1 (*Xenopus laevis* oocytes), OCT2, OCT3, OAT1, OAT2, OAT3 and OCTN1 [all expressed in HEK293 cells (Hu *et al.*, 2008)]. Recently, Eechoute *et al.* showed that imatinib is transported in *Xenopus laevis* oocytes and HeLa cells expressing OATP1A2 and this transport could be inhibited by rosuvastatin (Eechoute *et al.*, 2011a,b). First evidence that imatinib is a substrate of P-glycoprotein was provided by Hegedus *et al.* in 2002 (Hegedus *et al.*, 2002). Mahon *et al.* showed that a K562/DOX cell line overexpressing P-glycoprotein exhibited a reduced sensitivity to imatinib compared with the parental K562 cells (Mahon *et al.*, 2003). Studies using transfected MDCK cell lines revealed an active efflux component for imatinib attributable to P-glycoprotein (Thomas *et al.*, 2004). Hu *et al.* reported a weak but statistically significant interaction between imatinib and MRP4 (Hu *et al.*, 2008). In addition, imatinib was transported by BCRP in BCRP-overexpressing HEK293 and MCF7/MR cells (Burger *et al.*, 2004). Furthermore, Breedveld *et al.* showed that imatinib is transported by mouse Bcrp in MDCKII cells (Breedveld *et al.*, 2005). For imatinib, the brain-to-plasma ratios in *Abcg2*(–/–) mice were comparable with those in wild-type mice, whereas the brain-to-plasma ratios in *Abcb1a/1b*(–/–) and *Abcb1a/1b*(–/–) *Abcg2*(–/–) mice were more than 4- and 28-fold of those in wild-type mice, respectively (Zhou *et al.*, 2009). Dai *et al.* showed that the brain-to-plasma ratio in the *Abcb1a/1b*(–/–) mice was approximately sevenfold greater than that of wild-type mice, indicating that imatinib is a substrate of P-glycoprotein (Dai *et al.*, 2003).

Imatinib inhibited metformin uptake by MATE1, MATE2-K and OCT1 at potentially clinically relevant concentrations (Minematsu and Giacomini, 2011). The K_i value for the inhibition of P-glycoprotein function by imatinib was estimated to be 18.3 μM using a calcein-AM efflux assay in P-glycoprotein overexpressing pig kidney epithelial cells (LLC-PK1, Hamada *et al.*, 2003). Houghton *et al.* showed that imatinib significantly reversed BCRP-mediated resistance to topotecan and SN-38 and significantly increased accumulation of topotecan only in BCRP-expressing human osteosarcoma cells (Saos2, Houghton *et al.*, 2004). Imatinib inhibited BCRP-mediated mitoxantrone efflux in MCF7 and HEK293 cell lines overexpressing BCRP (Burger *et al.*, 2004). Furthermore, imatinib inhibited the MRP7-mediated efflux of paclitaxel in HEK293 cells (Shen *et al.*, 2009). The cellular uptake of nilotinib was increased by coadministration of imatinib *in vitro* due to P-glycoprotein and BCRP inhibition (White *et al.*, 2007b).

Multiple studies have been performed to elucidate associations between polymorphisms in genes encoding for drug metabolizing enzymes and drug transporters and pharmacokinetic parameters and/or clinical outcome (Table 4). It should be noted that in several studies the mean plasma concentrations or median minimum or 'trough' concentra-

tion (C_{min}) of imatinib were higher in responders compared with non-responders in the treatment of CML and GI stromal tumours [GIST; for review see (Eechoute *et al.*, 2011b)]. This indicates that the systemic concentrations of imatinib are correlated with the treatment outcome.

Very recently, Yamakawa *et al.* (2011) reported a significantly lower clearance of imatinib in patients with CML with *SLCO1A2* –361GG genotype compared with patients with –361 GA or AA genotypes. The pharmacogenetic data for the association of *SLC22A1* polymorphisms (*SLC22A1* encodes for OCT1) and pharmacodynamics of imatinib are inconsistent. One study demonstrated an increased risk for imatinib resistance due to loss of response and treatment failure in patients with CML, who are carriers of the c.480GG genotype in *SLC22A1* (Kim *et al.*, 2009), whereas a second study did not find any influence of this polymorphism on the major molecular response (Takahashi *et al.*, 2010). In the later study the c.1222GG genotype in *SLC22A1* was associated with higher rates of major molecular response in the treatment of CML with imatinib (Takahashi *et al.*, 2010).

In the last years different approaches were chosen to predict determinants of outcome in imatinib-treated patients. OCT1 was identified as a promising factor influencing the clinical outcome in the treatment with imatinib. A study by White *et al.* (2006) indicated that the intrinsic activity (defined as the *in vitro* concentration of drug required to reduce the phosphorylation of the adaptor protein Crkl by 50%) of newly diagnosed patients with CML to imatinib correlates with the molecular response. The intrinsic activity was mainly dependent from the intracellular uptake and retention of imatinib (White *et al.*, 2006). The uptake of imatinib into mononuclear cells was attributed to OCT1, because the uptake and retention was reduced by the OCT1 inhibitor prazosin (White *et al.*, 2006). Subsequent studies showed that the function or mRNA expression of OCT1 was associated with response to imatinib in patients with CML (White *et al.*, 2007a, 2010a,b; Wang *et al.*, 2008). It was consistently shown that a high OCT1 expression or function is related to a better response to imatinib treatment in CML patients compared with patients with a lower OCT1 expression or function. These studies suggest an association between the OCT1 expression and function with the prognosis in CML patients treated with imatinib. However, the underlying mechanism seems to be still not completely clarified, because a study by Hu and colleagues indicated that imatinib is only marginally transported by OCT1 (Hu *et al.*, 2008). This study also showed that the *SLC22A1* expression in leukaemia cell lines was interrelated with *SLCO1A2, ABCB1* and *ABCG2* mRNA expression (Hu *et al.*, 2008). Further studies are necessary to completely clarify the mechanism of OCT1-associated response to treatment with imatinib.

As mentioned above, imatinib is a substrate of P-glycoprotein and BCRP. Therefore, polymorphisms in the *ABCB1* and/or *ABCG2* genes could influence the intestinal absorption and elimination pathways. For BCRP, two studies revealed inconclusive associations between the c.421C>A polymorphism and clinical endpoints in the treatment of CML. In one study the c.421CC genotype was associated with a decreased complete molecular response, whereas a second study showed no relationship between this polymorphism and major molecular response (Takahashi *et al.*, 2010). In a further study with patients taking imatinib for the treatment of GIST no influence of the c.421C>A polymorphism on the oral clearance of imatinib was observed (Gardner *et al.*, 2006). Due to these results it can be concluded that additional studies enrolling a higher number of patients are needed in order to clarify the clinical relevance of this *ABCG2* c.421C>A polymorphism for the treatment of CML and GIST with imatinib.

The pharmacogenetic studies with regard to *ABCB1* polymorphisms and treatment outcome in CML patients are difficult to compare because the clinical endpoints and the investigated polymorphisms differ. Nevertheless, two studies revealed comparable results with respect to the c.3435C>T polymorphism (Kim *et al.*, 2009; Ni *et al.*, 2011). In a univariate analysis the c.3435TT genotype was associated with a decreased overall survival in patients with CML (Kim *et al.*, 2009). The second study showed a lower resistance to imatinib for the c.3435CC genotype (Ni *et al.*, 2011). Even though the analyses were performed either with patients with c.3435 wild-type genotype or homozygous carriers of the polymorphism (c.3435TT) and different clinical endpoints, both studies indicate that the c.3435C>T polymorphism impairs the response to imatinib treatment in CML.

Lapatinib

In vitro, lapatinib is a substrate of the efflux transporters P-glycoprotein and BCRP (Polli *et al.*, 2008). Based on a GF120918-treated rat model, Polli *et al.* (2008) concluded that lapatinib disposition after oral administration is not affected when P-glycoprotein and Bcrp are absent. Similar to other tyrosine kinase inhibitors (e.g. dasatinib), brain penetration of lapatinib is affected by P-glycoprotein and Bcrp. It was shown using knockout mouse models that the brain-to-plasma concentration ratios in *Abcb1a/1b* and *Abcb1a/1b Abcg2* knockout mice were three- to fourfold and 40-fold respectively, higher compared with wild-type mice, whereas there was no significant effect in *Abcg2* knockout mice compared with wild-type mice (Polli *et al.*, 2009).

In vitro data indicate that lapatinib is an inhibitor of OATP1B1 function at clinically relevant concentrations (Polli *et al.*, 2008; Fachinformation, 2010). Currently, there are no data on the impact of lapatinib on plasma concentrations of OATP1B1 substrates in humans. In contrast, lapatinib had little effects on OAT1 to 4 and OCT1 to 3 (Polli *et al.*, 2008; Minematsu and Giacomini, 2011). Lapatinib inhibits the efflux transporters P-glycoprotein, BCRP and MRP7 *in vitro* (Dai *et al.*, 2008; Molina *et al.*, 2008; Kuang *et al.*, 2010; Perry *et al.*, 2010). It was speculated that these properties might be advantageous for concomitant treatment of lapatinib with conventional chemotherapeutic drugs, whose effects are limited due to multidrug resistance mediated in part via transporter-mediated efflux. Molina *et al.* (2008) recently showed that the combination of lapatinib with the P-glycoprotein/BCRP substrate topotecan showed enhanced efficacy in human breast carcinoma xenografts. Moreover, lapatinib moderately reduced topotecan clearance in patients (Molina *et al.*, 2008). In line with the inhibition of P-glycoprotein function by lapatinib *in vitro*, lapatinib

increased the AUC after oral administration of the P-glycoprotein substrate digoxin by 80% (Fachinformation, 2010).

Nilotinib

Nilotinib is not transported by OCT1 (White *et al.*, 2006; Davies *et al.*, 2009). There are conflicting data whether nilotinib is a substrate of BCRP or P-glycoprotein. Mahon *et al.* reported by reversing the resistance of K562/DOX cells to nilotinib with verapamil or PSC833 that nilotinib is a substrate of P-glycoprotein (Mahon *et al.*, 2008). Haouala *et al.* (2010), however, did not observe an impact of P-glycoprotein silencing on cellular nilotinib disposition. Hegedus *et al.* (2009) reported that nilotinib is a high-affinity substrate of BCRP. Brendel *et al.* (2007) described nilotinib as a modest BCRP substrate. Finally, the data from Davies *et al.* (2009) indicate that nilotinib is not transported by BCRP, MRP1 and P-glycoprotein.

OCT3-mediated metformin uptake in HEK293 cells was potently inhibited by nilotinib with an IC_{50} value of 0.345 μM (Minematsu and Giacomini, 2011). Nilotinib was also an inhibitor of OCT1 (Davies *et al.*, 2009; Minematsu and Giacomini, 2011), but probably at clinically less relevant concentrations (Minematsu and Giacomini, 2011). Nilotinib inhibited the BCRP/Bcrp-mediated Hoechst 33342 dye efflux from primary human and murine haematopoietic stem cells (HSCs; Brendel *et al.*, 2007). Several groups showed that nilotinib is an inhibitor of BCRP and P-glycoprotein (Davies *et al.*, 2009; Tiwari *et al.*, 2009; Dohse *et al.*, 2010). Nilotinib was a more potent inhibitor of BCRP and P-glycoprotein compared with imatinib and dasatinib (Dohse *et al.*, 2010). Hiwase *et al.* reported that inhibition of P-glycoprotein by nilotinib increased dasatinib accumulation in CML cells with potential implications for combination therapy with tyrosine kinase inhibitors (Hiwase *et al.*, 2010). Similar to imatinib, nilotinib reversed MRP7-mediated paclitaxel resistance, most likely due to inhibition of MRP7-mediated paclitaxel efflux (Shen *et al.*, 2009).

Pazopanib

In vitro studies indicate that pazopanib is a substrate of BCRP and P-glycoprotein [US Food and Drug Administration (FDA), 2010b]. The uptake transporter OATP1B1 is potently inhibited by pazopanib with an IC_{50} value of 0.79 μM and may therefore increase serum concentrations of concomitantly administered OATP1B1 substrates such as 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG-CoA) reductase inhibitors (FDA, 2010b; Keisner and Shah, 2011). Coadministration of lapatinib, a weak inhibitor of CYP3A4 and an inhibitor of P-glycoprotein and BCRP, with pazopanib resulted in a 50–60% increase in mean pazopanib AUC compared with the administration of pazopanib alone (FDA, 2010b).

Sorafenib

Sorafenib is highly permeable (Gnoth *et al.*, 2010) and *in vitro* uptake of sorafenib is not affected by major OATPs, OCT1, OAT2, OAT3 and OCTNs (Hu *et al.*, 2009). Sorafenib is a weak P-glycoprotein substrate *in vitro* (Hu *et al.*, 2009; Gnoth *et al.*, 2010; Haouala *et al.*, 2010; Lagas *et al.*, 2010; Agarwal *et al.*, 2011), but is more efficiently transported by BCRP/Bcrp (Lagas *et al.*, 2010; Agarwal *et al.*, 2011). In knockout mouse models, plasma concentrations of sorafenib were largely unaffected in the absence of P-glycoprotein and/or Bcrp (Gnoth *et al.*, 2010; Lagas *et al.*, 2010; Agarwal *et al.*, 2011). Sorafenib brain concentrations increased to some extent in P-glycoprotein deficient animals compared with wild-type mice, but the increase was considerably higher in the absence of Bcrp with the most pronounced effect in P-glycoprotein/Bcrp-deficient animals (Hu *et al.*, 2009; Gnoth *et al.*, 2010; Lagas *et al.*, 2010; Agarwal *et al.*, 2011; Asakawa *et al.*, 2011). This observed interplay of P-glycoprotein and Bcrp *in vivo* was recently also observed in double-transfected MDCK-BCRP-P-glycoprotein cells (Poller *et al.*, 2011). Sorafenib was also reported to be a substrate of MRP2 in one study (Shibayama *et al.*, 2011), which might play a role for anticancer drug resistance to sorafenib, but no transport of sorafenib by MRP2 (and by BCRP and MRP4) was found in another study (Hu *et al.*, 2009). Sorafenib inhibits P-glycoprotein, MRP2 and MRP4 function *in vitro*, whereas BCRP inhibition by sorafenib appears to be substrate-dependent (Hu *et al.*, 2009; Agarwal *et al.*, 2011).

Sunitinib

Similar to sorafenib, *in vitro* uptake of sunitinib was not mediated by major uptake transporters (OATPs, OCT1, OAT2, OAT3 and OCTNs; Hu *et al.*, 2009). *In vitro*, sunitinib is a substrate of P-glycoprotein, BCRP, possibly of MRP4 and a good substrate of Bcrp, but it is not transported by MRP2 (Hu *et al.*, 2009; Shibayama *et al.*, 2011; Tang *et al.*, 2011). In mice, brain sunitinib accumulation is restricted by P-glycoprotein (Hu *et al.*, 2009) and Bcrp and could be enhanced by the dual P-glycoprotein/Bcrp inhibitor elacridar (Tang *et al.*, 2011).

Sunitinib inhibits P-glycoprotein and BCRP function *in vitro* with possible consequences for bioavailability of coadministered drugs and for reversing efflux transporter-mediated multidrug resistance in humans (Dai *et al.*, 2009; Hu *et al.*, 2009; Shukla *et al.*, 2009; Kawahara *et al.*, 2010). Interestingly, a germ-line mutation in *ABCG2* (c.1291T>C) is almost insensitive to sunitinib-mediated inhibition in a cell proliferation assay (Kawahara *et al.*, 2010).

In a small study it was reported that the *ABCG2* c.421AA genotype, which is associated with higher plasma concentrations of several drugs (Poguntke *et al.*, 2010), was also associated with higher sunitinib concentrations in a patient with renal cell carcinoma compared with patients having the CA or CC genotype (Mizuno *et al.*, 2010). van der Veldt *et al.* (2011) reported in a recent retrospective pharmacogenetic association study in 136 patients with clear-cell metastatic renal cell carcinoma that the TCG haplotype of *ABCB1* (c.3435C>T, c.1236C>T, c.2677G>T) was together with variants in *CYP3A5* and *NR1I3* significantly associated with improved progression-free survival. In addition there was a trend for improved outcome in the presence of the A allele of the *ABCG2* c.34G>A variant. Moreover, van Erp *et al.* (2009a) reported in a study with 219 sunitinib treated patients that

prevalence of any toxicity higher than grade 2 according to the National Cancer Institute Common Toxicity Criteria was increased in patients with a copy of TT in *ABCG2* (-15622C>T, c.1143C>T) haplotype (OR = 2.63, $P = 0.016$). Moreover, the prevalence of hand-foot syndrome was increased when a copy of TTT in the *ABCB1* (c.3435C>T, c.1236C>T, c.2677G>T) haplotype (OR = 2.56; $P < 0.035$) was present (van Erp *et al.*, 2009a).

Everolimus

The mTOR inhibitor everolimus is a substrate of CYP3A4 and of P-glycoprotein (Crowe and Lemaire, 1998; FDA, 2011), but not of OATP uptake transporters (OATP1A2, OATP1B1, OATP1B3; Picard *et al.*, 2011). AUC after oral administration of everolimus to P-glycoprotein-deficient mice was increased 1.3-fold compared with wild-type animals (Chu *et al.*, 2009). In P-glycoprotein expressing mice the tyrosine kinase inhibitor lapatinib increased everolimus AUC 2.6-fold, in part due to reducing intestinal P-glycoprotein expression (Chu *et al.*, 2009).

In vitro, everolimus was an inhibitor of OATP1A2, OATP1B1 and OATP1B3 function determined by uptake of prototypical substrates such as estrone sulphate and mycophenolic acid 7-*O*-glucuronide with IC_{50} values in the low micromolar range (Picard *et al.*, 2011). In healthy volunteers a single oral dose of 2 mg everolimus had no influence on the AUC (Kovarik *et al.*, 2002) of the OATP1B1 and OATP1B3 substrate pravastatin (20 mg; Seithel *et al.*, 2007; Fahrmayr *et al.*, 2010). It should be noted, however, that the recommended daily dose of everolimus in cancer patients is 10 mg per day, that is, it cannot be excluded that everolimus at this higher dose used in cancer patients (and during steady-state) has effects on pharmacokinetics of pravastatin and potentially of other OATP substrates.

Temsirolimus

Temsirolimus and sirolimus, its principal metabolite in humans after intravenous administration, are substrates of CYP3A4 (FDA, 2010a). Sirolimus is a substrate of P-glycoprotein (Crowe and Lemaire, 1998). Similar to everolimus, sirolimus is an inhibitor, but not a substrate of OATP uptake transporters (OATP1A2, OATP1B1, OATP1B3; Picard *et al.*, 2011).

In vitro data indicate that temsirolimus is an inhibitor of P-glycoprotein (Fachinformation, 2011). Zimmerman *et al.* reported that sirolimus did not significantly affect plasma concentrations of the P-glycoprotein substrate digoxin in healthy volunteers (Zimmerman, 2004). Currently, there are no data available regarding the impact of temsirolimus on plasma concentrations of digoxin or of the OATP substrate pravastatin in humans.

Bortezomib

Very limited data are currently available regarding the interaction of the proteasome inhibitor bortezomib with drug transporters. *In vitro* data from Rumpold *et al.* (2007) indicate that bortezomib is a moderate substrate of P-glycoprotein. In a subgroup of patients with advanced multiple myeloma treated with bortezomib alone, no association between outcome and *ABCB1* or *ABCC1* polymorphisms was found (Buda *et al.*, 2010).

Conclusions

In vitro data indicate that most of the small molecules discussed in this review are substrates of the efflux transporters BCRP and/or P-glycoprotein. The relevance of Bcrp and P-glycoprotein for brain concentrations was clearly highlighted using knockout mouse models. Intracellular concentrations of some tyrosine kinase inhibitors might also depend on uptake transporters. *In vitro* data also indicate that the majority of the small molecules inhibit uptake and/or efflux transporters with potential consequences for the occurrence of drug–drug interactions. For some of the tyrosine kinase inhibitors pharmacogenetic association studies were conducted, showing an impact of certain polymorphisms in genes encoding drug transporters with disposition and effects. Considerably more data are necessary, to show how this interaction of small molecules with drug transporters is relevant for the clinical situation. This relates to clinical investigations of transporter-mediated drug interactions (e.g. with metformin), the importance of efflux transporter inhibition by small molecules for the reversal of multidrug resistance and on pharmacogenetic factors determining interindividual differences in efficacy and toxicity of the new small molecules.

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Conflict of interest

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