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Organic Anion Transporting Polypeptide 1B1: a Genetically Polymorphic Transporter of Major Importance for Hepatic Drug Uptake

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***Abstract*——The importance of membrane transporters for drug pharmacokinetics has been increasingly recognized during the last decade. Organic anion transporting polypeptide 1B1 (OATP1B1) is a genetically polymorphic influx transporter expressed on the sinusoidal membrane of human hepatocytes, and it mediates the hepatic uptake of many endogenous compounds and xenobiotics. Recent studies have demonstrated that OATP1B1 plays a major, clinically important role in the hepatic uptake of many drugs. A common single-nucleotide variation (coding DNA c.521T>C, protein p.V174A, rs4149056) in the *SLCO1B1* gene encoding OATP1B1 decreases the transporting activity of OATP1B1, resulting in markedly increased plasma concentrations of, for example, many statins, particularly of active simvastatin acid. The variant thereby enhances the risk of statin-induced myopathy and decreases the therapeutic indexes of statins. However, the effect of the *SLCO1B1* c.521T>C variant is different on different statins. The same variant also markedly affects the pharmacokinetics of several other drugs. Furthermore, certain *SLCO1B1* variants associated with an enhanced clearance of methotrexate increase the risk of gastrointestinal toxicity by methotrexate in the treatment of children with acute lymphoblastic leukemia. Certain drugs (e.g., cyclosporine) potently inhibit OATP1B1, causing clinically significant drug interactions. Thus, OATP1B1 plays a major role in the hepatic uptake of drugs, and genetic variants**

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and drug interactions affecting OATP1B1 activity are important determinants of individual drug responses. In this article, we review the current knowledge about the expression, function, substrate characteristics, and pharmacogenetics of OATP1B1 as well as its role in drug interactions, in parts comparing with those of other hepatocyte-expressed organic anion transporting polypeptides, OATP1B3 and OATP2B1.

I. Introduction

Transporters are integral membrane proteins that mediate the translocation of chemicals into and out of cells using active and passive mechanisms (Klaassen and Aleksunes, 2010). More than 400 membrane transporters in two major superfamilies, ATP-binding cassette and solute carrier, have been annotated in the human genome (Giacomini et al., 2010). Many of these transporters have been characterized at the molecular level and localized to tissues and cellular membrane domains in the human body.

The past 10 years have seen an enormous increase in the literature concerning the role of membrane transporters in governing drug pharmacokinetics and response (Giacomini et al., 2010). Influx and efflux transporters expressed on the plasma membranes of polarized cells in tissues important for pharmacokinetics have been shown to significantly affect the absorption, tissue distribution, and elimination of drugs. Transporters are now known to be partially responsible for determining the concentrations of drugs in plasma and peripheral tissues, thus affecting drug efficacy and toxicity.

Access into the liver is an important step preceding the elimination of many endogenous compounds and xenobiotics, including most drugs. Organic anion-transporting polypeptide 1B1 (OATP1B1[1]; previously known as OATP2, OATP-C, and liver-specific transporter 1) is one of the main influx transporters expressed on the basolateral membrane of human hepatocytes (Kalliokoski and Niemi, 2009; Fahrmayr et al., 2010; Giacomini et al., 2010; Klaassen and Aleksunes, 2010). Here we aim to review the current knowledge about the expression, function, substrate characteristics, and pharmacogenetics of OATP1B1 as well as its role in drug interactions. When appropriate, these will be compared with the characteristics of other hepatocyte-expressed OATPs, OATP1B3 and OATP2B1.

[1]Abbreviations: AUC, area under the plasma concentration-time curve; BCRP, breast cancer resistance protein; bp, base pair(s); C_{max}, peak plasma concentration; FXR, farnesoid X receptor; HNF, hepatocyte nuclear factor; IC_{50}, inhibitor concentration producing 50% inhibition of transporter activity; kb, kilobase(s); MRP, multidrug resistance-associated protein; OATP, organic anion transporting polypeptide; PXR, pregnane X receptor; *SLCO*, solute carrier organic anion transporter gene; SN-38, 7-ethyl-10-hydroxy-camptothecin; SNP, single-nucleotide polymorphism.

II. Basic Characteristics of Organic Anion-Transporting Polypeptide 1B1

A. Genomic Organization

Genes encoding organic anion-transporting polypeptides form a large family of solute carrier organic anion transporter genes (*SLCO*) within the solute carrier superfamily (Hagenbuch and Meier, 2004). Based on phylogenetic relationships and chronology of identification, OATPs have been divided into families designated in the current nomenclature by an Arabic numeral (e.g., OATP1/*SLCO1*); individual proteins share more than 40% of their amino acid sequence identity, and subfamilies designated by a capital letter (e.g., OATP1B/*SLCO1B*) share more than 60% amino acid sequence identity. The individual gene products and genes are designated by an Arabic numeral: OATP1B1/*SLCO1B1* (Hagenbuch and Meier, 2004).

More than 150 *SLCO*s have been annotated in animal genomes, with 11 human *SLCO*s belonging to six families (Hagenbuch and Meier, 2004). In general, *SLCO* family members are poorly conserved evolutionarily, and orthologs for human OATP1B1 may not exist in rodents. Dogs have only one Oatp1b family member, Oatp1b4, and the extrapolation of liver uptake from dogs to humans may also be difficult (Gui and Hagenbuch, 2010). The *SLCO1* family is the largest human family, comprising the genes encoding the first cloned human OATP, OATP1A2 (Kullak-Ublick et al., 1995), as well as OATP1B1, OATP1B3, and OATP1C1. These genes are located in a cluster in the short arm of chromosome 12 (Fig. 1) (Kullak-Ublick et al., 1996; König et al., 2000a). The *SLCO1B1* gene spans a region of 108.59 kb and consists of 14 coding exons and one noncoding exon, designated in this review as exon as −1, located 10.277 kb upstream from the first coding exon. The *SLCO1B1* gene encodes a 2791-bp mRNA (NM_006446) containing a 95-bp 5′-untranslated region and a 621-bp 3′-untranslated region. To date, no splice variants have been described for *SLCO1B1*.

B. Structure

OATP1B1 is a 691-amino acid glycoprotein; it contains, on the basis of hydropathy analyses, 12 putative membrane-spanning domains and a large fifth extracellular loop (König et al., 2000b; Hagenbuch and Meier, 2003; Chang et al., 2005; Niemi, 2007) (Fig. 2). OATP1B1 carries *N*-glycosylation sites common to all OATPs in extracellular loops 2 and 5 and the OATP superfamily signature D-X-RW-(I,V)-GAWW-X-G-(F,L)-L at the border between the predicted extracellular loop 3 and the transmembrane domain 6. OATP1B1 shares 80% amino acid identity with

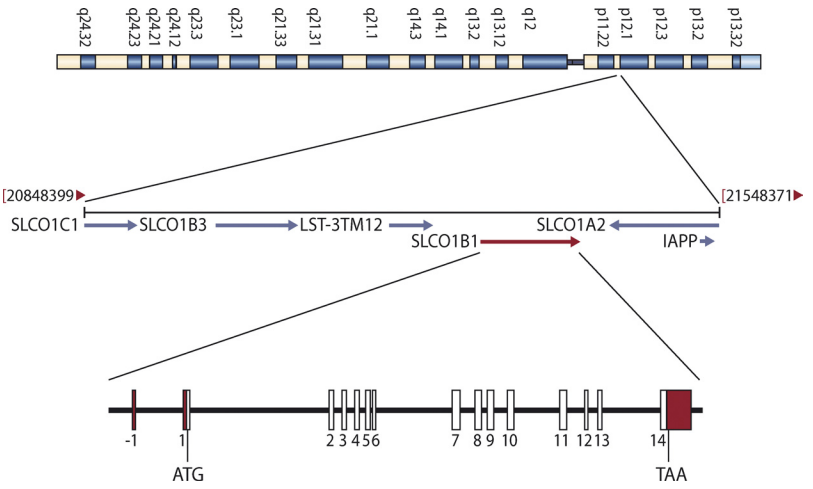

FIG. 1. The *SLCO1B1* gene is localized to an *SLCO1* gene cluster in the short arm of chromosome 12.

OATP1B3 (König et al., 2000a). Its apparent molecular mass is 84 kDa, which is reduced after deglycosylation to 58 kDa (König et al., 2000b).

C. Expression and Transcriptional Regulation

At the mRNA level, *SLCO1B1* is expressed mainly in the liver (Abe et al., 1999; Hsiang et al., 1999; König et al., 2000a,b), although small amounts of SLCO1B1 mRNA have also been detected in several other tissues, such as the small intestine (Glaeser et al., 2007; Klaassen and Aleksunes, 2010). At the protein level, OATP1B1 is found only in the liver, where it has been localized to the basolateral membrane of hepatocytes (König et al., 2000b) (Fig. 3). In addition to OATP1B1, two other OATPs, OATP1B3 and OATP2B1, are also highly expressed in human liver (König et al., 2000a; Kullak-Ublick et al., 2001). OATP1B1 shows a uniform expression pattern throughout liver sections, whereas the expression of the closely related OATP1B3 is more restricted, showing the highest expression in perivenous regions (Ho et al., 2006).

The promoter region upstream of the exon −1 of the *SLCO1B1* gene contains several consensus recognition sites for both ubiquitously expressed and liver-enriched transcription factors, including hepatocyte nuclear factor 1 (HNF1), HNF3, CCAAT-enhancer binding protein, and activator protein 1 (Jung et al., 2001). Transfection experiments with *SLCO1B1* promoter constructs in hepatic (HepG2, Huh7) and nonhepatic (HeLa) cell lines have demonstrated basal promoter activity only in hepatocyte-derived cell lines. DNase I footprinting experiments as well as mobility shift and supershift assays have identified a binding site for HNF1 in the proximal promoter region. Coexpression of exogenous HNF1A has stimulated *SLCO1B1* promoter activity up to 30-fold in HepG2 cells and produced basal promoter activity even in HeLa cells. Moreover, targeted mutation of the HNF1 binding site has abolished not only inducibility of the *SLCO1B1* promoter by HNF1A, but even the basal promoter function in HepG2 cells (Jung et al., 2001). Moreover, the mRNA expression of *SLCO1B1* showed a

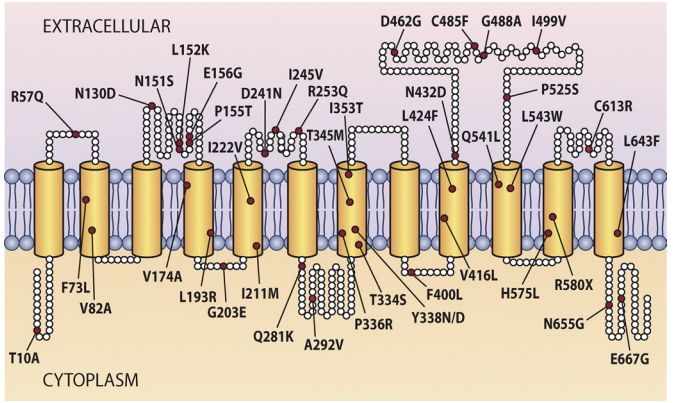

FIG. 2. The predicted transmembrane structure of OATP1B1, depicting the positions of nonsynonymous single nucleotide polymorphisms.

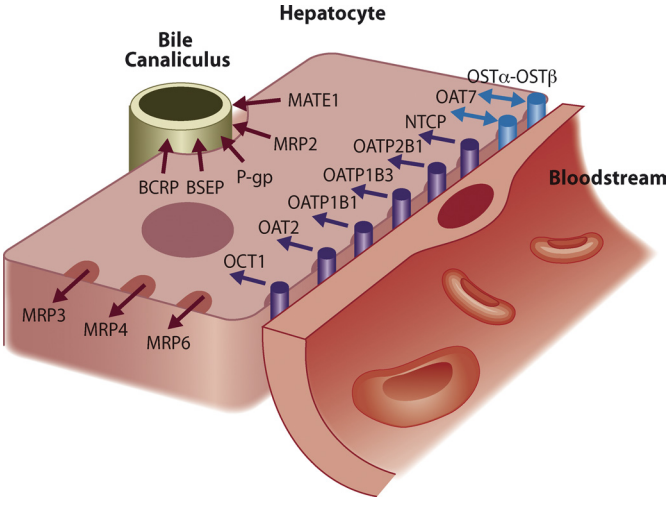

FIG. 3. Selected transporters for endogenous compounds and xenobiotics, expressed on the sinusoidal and canalicular membranes of human hepatocytes (for review, see Giacomini et al., 2010; Klaassen and Aleksunes, 2010). BSEP, bile salt export pump; MATE1, multidrug and toxin extrusion protein 1; NTCP, sodium/taurocholate cotransporting peptide; OAT, organic anion transporter; OCT, organic cation transporter; OSTα-OSTβ, heteromeric organic solute transporter.

strong correlation with the expression level of *HNF1A* in one study in Japanese adult liver samples (Furihata et al., 2007). Taken together, these data indicate that HNF1A plays a crucial role in the hepatocyte-specific expression of OATP1B1.

In two studies, SLCO1B1 mRNA expression was induced in primary human hepatocytes by approximately 2.3- to 2.4-fold by rifampin (International Nonproprietary Name, rifampicin) (Jigorel et al., 2006; Sahi et al., 2006), a pregnane X receptor (PXR, *NR1I2*) ligand and known clinical inducer of many drug-metabolizing enzymes (Lehmann et al., 1998; Niemi et al., 2003a). These data suggest that PXR regulates the inducible expression of OATP1B1. Nevertheless, induction of *SLCO1B1* by rifampin is much weaker than, for example, that of the drug-metabolizing cytochrome P450 3A4 (CYP3A4) (Jigorel et al., 2006; Sahi et al., 2006). *SLCO1B1* expression has been found to be regulated by the bile acid-sensing nuclear receptor farnesoid X receptor (FXR, *NR1H4*) and the oxysterol-sensing liver X receptor α (*NR1H3*) (Meyer zu Schwabedissen et al., 2010). FXR ligands (e.g., chenodeoxycholic acid) might thus increase OATP1B1 expression and enhance the hepatic uptake of OATP1B1 substrates.

D. Function

The almost exclusive expression of OATP1B1 protein in human hepatocytes suggests that it plays a crucial role in the hepatic uptake and clearance of albumin-bound amphipathic organic compounds. The mechanism of its substrate transport is not completely understood, although it has been suggested that OATPs translocate their substrates through a central, positively charged pore in a so-called rocker-switch type of mechanism (Meier-Abt et al., 2005). The transport is thought to be electroneutral and is independent of sodium, chloride, and potassium gradients; membrane potential; and ATP levels. No high resolution structures are presently available for OATP1B1, but according to one study using three-dimensional quantitative structure-activity relationship models, OATP1B1 substrates produce a pharmacophore containing two hydrogen bond acceptors, one hydrogen bond donor, and two hydrophobic regions (Hagenbuch and Meier, 2004; Chang et al., 2005). In another study using a meta-pharmacophore approach by combining limited data sets from different laboratories, cell types and species, a meta-model for OATP1B1 was generated in which the hydrophobic features are centrally located and the hydrogen bond features are located at the extremities (Chang et al., 2005). Site-directed mutagenesis studies of conserved positively charged amino acid residues identified arginine at position 57, lysine at position 361, and arginine at position 580 to be important for the substrate binding or translocation by OATP1B1 (Weaver and Hagenbuch, 2010). It is noteworthy that the transport of some OATP1B1 substrates, such as estrone-3-sulfate and 17α-ethinylestradiol sulfate, shows biphasic kinetics suggesting the possibility of multiple substrate binding sites in OATP1B1 (Noé et al., 2007; Han et al., 2010).

III. Substrates of Organic Anion Transporting Polypeptide 1B1

OATP substrates are often anionic amphipathic molecules with a relatively high molecular weight (>350) and a high degree of albumin binding under physiological conditions (Hagenbuch and Meier, 2004). The high degree of amino acid similarity between OATP1B1 and OATP1B3 translates into an overlapping substrate specificity in these transporters (Kullak-Ublick et al., 2001; Kalliokoski and Niemi, 2009; Fahrmayr et al., 2010). Clear differences have also been found in the substrate specificities of OATP1B1 and OATP1B3; e.g., paclitaxel and docetaxel are substrates of OATP1B3 only (Smith et al., 2005).

In vitro assessment of OATP1B1 function depends on a number of transient and stable heterologous expression systems (Giacomini et al., 2010). These include *Xenopus laevis* oocytes and recombinant virus-infected or stably transfected cell lines expressing OATP1B1 (Tables 1 and 2). In these experiments, the cellular uptake seen in *SLCO1B1*-transfected cells is compared with that observed in cells transfected with vector only. In addition, stable expression of OATP1B1 in combination with efflux transporters [e.g., multidrug resistance-associated protein (MRP) 2, P-glycoprotein, and breast cancer resistance protein (BCRP)] in polarized cells has been employed to study influx and efflux transporter interplay in the transcellular transport of chemicals (Kopplow et al., 2005; Matsushima et al., 2005). Isolated hepatocytes with OATP inhibitors have also been used to study OATP1B1 function, especially in comparison with OATP1B3 and OATP2B1 (Noé et al., 2007). Furthermore, in vivo disposition of endogenous compounds and drugs has been reported for *Slco1b2*(−/−), *Slco1a/1b*(−/−), and *SLCO1B1* transgenic mouse models (Lu et al., 2008; Zaher et al., 2008; van de Steeg et al., 2009, 2010). Data from *Slco1b2*(−/−) mice may partly reflect the activity of both human OATP1B1 and OATP1B3, and those from *Slco1a/1b*(−/−) knockout mice may more comprehensively reflect hepatic OATP uptake transporters, but additional studies are needed to confirm the utility of rodent models to predict the function of human OATP1B1.

A. Endogenous Compounds

In studies employing various transiently or stably OATP1B1-expressing cell lines, several bile acids, such as the primary bile acid cholic acid as well as secondary bile acids, such as glycocholic acid, glycoursodeoxycholic acid, taurocholic acid, and tauroursodeoxycholic acid, have been identified as OATP1B1 substrates (Abe et al., 1999; Hsiang et al., 1999; König et al., 2000b; Cui et al.,

TABLE 1
Endogenous substrates of OATP1B1

Substrate	K_m	Expression System	Reference
	μM		
Bile acids			
Cholic acid	11	HEK293	Cui et al., 2001
Glycocholic acid	+	XO	Kullak-Ublick et al., 2001
Glycoursodeoxycholic acid	+	HEK293	Maeda et al., 2006b
Taurolithocholic acid 3-sulfate	+	MDCKII	Sasaki et al., 2002
Taurocholic acid	34	HEK293c18	Hsiang et al., 1999
	14	XO	Abe et al., 1999
	+	HEK293	König et al., 2000b
	10	HEK293	Cui et al., 2001
Tauroursodeoxycholic acid	+	HEK293	Maeda et al., 2006b
Thyroid hormones			
Thyroxine	+	HEK293c18	Hsiang et al., 1999
	3.0	XO	Abe et al., 1999
Triiodothyronine	2.7	XO	Abe et al., 1999
Iodothyronine sulfates	+	COS1	van der Deure et al., 2008
Eicosanoids			
Leukotriene C_4	+	XO	Abe et al., 1999
Leukotriene E_4	+	XO	Abe et al., 1999
Prostaglandin E_2	+	XO	Abe et al., 1999
	+	HEK293	Tamai et al., 2000
Thromboxane B_2	+	XO	Abe et al., 1999
Others			
Bilirubin	0.16	HEK293	Cui et al., 2001
	0.0076	XO	Briz et al., 2003
Bilirubin monoglucuronide	0.1	HEK293	Cui et al., 2001
Bilirubin diglucuronide	0.3	HEK293	Cui et al., 2001
CCK-8	+	HEK293	Hirano et al., 2004
DHEAS	+	XO	Abe et al., 1999
	22	HEK293	Cui et al., 2001
$E_2$17βG	+	XO	Abe et al., 1999
	8.2	HEK293	König et al., 2000b
	9.7	XO	Nakai et al., 2001
	3.7	XO	Tamai et al., 2001
	8.2	HEK293	Cui et al., 2001
	28	MDCKII	Sasaki et al., 2002
	8.3	HEK293	Hirano et al., 2004
	6.3	HEK293	Sharma et al., 2009
E_1S	+	XO	Abe et al., 1999
	0.2	HEK293	Tamai et al., 2000
	5.3	XO	Tamai et al., 2001
	13	HEK293	Cui et al., 2001
	0.5	HEK293	Hirano et al., 2004
	+	MDCKII	Kopplow et al., 2005
	0.23, 45	HEK293	Noé et al., 2007
	+	COS1	van der Deure et al., 2008
	+	Flp-In-293	Nakakariya et al., 2008

CCK-8, cholecystokinin octapeptide; CHO, Chinese hamster ovary; DADLE, [D-Ala^2,D-Leu^5]-enkephalin (opioid peptide analog); DHEAS, dehydroepiandrosterone sulfate; $E_2$17βG, estradiol-17β-D-glucuronide; E_1S, estrone-3-sulfate; HEK293, human embryonic kidney 293 cells; HepG2, a human liver carcinoma cell line; MDCKII, Madin-Darby canine kidney cells; XO, *Xenopus laevis* oocyte; +, substrate of OATP1B1, but K_m not available.

2001; Kullak-Ublick et al., 2001; Maeda et al., 2006b) (Table 1). In addition, a fluorescently labeled derivative of chenodeoxycholic acid is transported by OATP1B1, suggesting that this primary bile acid is also an OATP1B1 substrate (Yamaguchi et al., 2006). OATP1B1 seems to represents the main sodium-independent uptake mechanism for bile acids in the liver. OATP1B1 can transport also both unconjugated and conjugated bilirubin (Cui et al., 2001). Although OATP1B3 is also capable of bilirubin transport, OATP1B1 seems to be more important for unconjugated bilirubin (Cui et al., 2001).

Thyroid hormones are substrates of OATP1B1 (Abe et al., 1999; Hsiang et al., 1999; van der Deure et al., 2008), which may be primarily responsible for the hepatic uptake of these compounds. Several eicosanoids, cholecystokinin octapeptide, dehydroepiandrosterone sulfate, estradiol-17β-D-glucuronide, and estrone-3-sulfate are substrates of OATP1B1 (Abe et al., 1999; König et al., 2000b; Tamai et al., 2000; Cui et al., 2001; Nakai et al., 2001; Tamai et al., 2001; Sasaki et al., 2002; Hirano et al., 2004; Kopplow et al., 2005; Nakakariya et al., 2008; van der Deure et al., 2008; Sharma et al., 2009), the last two being commonly employed as OATP1B1 model substrates in in vitro experiments.

B. Drugs

Drugs from several important therapeutic classes have been identified as OATP1B1 substrates (Table 2). One of the first identified drug substrates for OATP1B1 was the HMG-CoA reductase inhibitor pravastatin (Hsiang et al., 1999) used in the treatment of hypercholesterolemia. It is now known that all statins in clinical

TABLE 2
Xenobiotic substrates of OATP1B1

Substrate	K_m	Expression System	Reference
	μM		
Antibacterials			
Benzylpenicillin	+	HEK293	Tamai et al., 2001
Cefditoren	3.45	XO	Nakakariya et al., 2008
Cefoperazone	4.84	XO	Nakakariya et al., 2008
Cefazolin	20.8	XO	Nakakariya et al., 2008
Nafcillin	11.1	XO	Nakakariya et al., 2008
Rifampin	13	XO	Vavricka et al., 2002
	1.5	HeLa	Tirona et al., 2003
Anticancer drugs			
Gimatecan	+	MDCKII	Oostendorp et al., 2009
SN-38	+	XO	Nozawa et al., 2005
Pazopanib	+		European Medicines Agency, 2010b
Lipid-lowering drugs			
Atorvastatin	12.4	HEK293	Kameyama et al., 2005
Cerivastatin	+	MDCKII	Shitara et al., 2003
	+	HEK293	Kameyama et al., 2005
Ezetimibe glucuronide	+	HEK293	Oswald et al., 2008
Fluvastatin	2.4	MDCKII	Kopplow et al., 2005
	31	XO	Deng et al., 2008a
	1.4, 3.5	CHO	Noé et al., 2007
Pitavastatin	3.0	HEK293	Hirano et al., 2004
	6.7	XO	Deng et al., 2008a
Pravastatin	35	HEK293	Hsiang et al., 1999
	11.5	XO	Nakai et al., 2001
	24	MDCKII	Sasaki et al., 2002
	86	HEK293	Kameyama et al., 2005
	58	XO	Deng et al., 2008a
	109	HEK293	Furihata et al., 2009
Rosuvastatin	7.3	XO	Brown et al., 2001
	+	XO	Simonson et al., 2004
	8.5	XO	Schneck et al., 2004
	4.0	HeLa	Ho et al., 2006
	0.802	HEK293	Kitamura et al., 2008
Other cardiovascular drugs			
Bosentan	44	CHO	Treiber et al., 2007
Enalapril	262	HEK293	Liu et al., 2006
Olmesartan	42.6	XO	Nakagomi-Hagihara et al., 2006
	12.8	HEK293	Yamada et al., 2007
Valsartan	+	HEK293	Maeda et al., 2006a
	1.39	HEK293	Yamashiro et al., 2006
	17.8	CHO	Poirier et al., 2009
Temocapril	+	HEK293	Maeda et al., 2006a
Torsemide	6.2	HEK293	Werner et al., 2010
HIV protease inhibitors			
Darunavir	+	XO	Hartkoorn et al., 2010
Lopinavir	+	XO	Hartkoorn et al., 2010
Saquinavir	+	XO	Hartkoorn et al., 2010
Other drugs, diagnostic markers, and drugs under development			
ACU154	+	MDCKII	Takada et al., 2004
Atrasentan	+	HeLa	Katz et al., 2006
Bamet-UD2	10	XO	Briz et al., 2002
Bamet-R2	10	XO	Briz et al., 2002
Bromosulfophthalein	0.1	HEK293	Cui et al., 2001
	0.3	XO	Kullak-Ublick et al., 2001
	2.4	MDCKII	Kopplow et al., 2005
	+	COS1	van der Deure et al., 2008
BQ-123	+	XO	Kullak-Ublick et al., 2001
Caspofungin	+	HeLa	Sandhu et al., 2005
DADLE	+	XO	Nozawa et al., 2003
DPDPE	+	XO	Kullak-Ublick et al., 2001
	+	XO	Abe et al., 2001
EE2S	0.087, 141	HEK293	Han et al., 2010
Fexofenadine	+	MDCKII	Matsushima et al., 2008
Flavopiridol	+	HEK293	Ni et al., 2010
Flavopiridol-glucuronide	+	HEK293	Ni et al., 2010
Gd-EOB-DTPA	700	HEK293	Leonhardt et al., 2010
Karenitecin (BNP1350)	+	MDCKII	Oostendorp et al., 2009
Methotrexate	+	XO	Abe et al., 2001
Mycophenolic acid-*O*-glucuronide	+	HEK293	Picard et al., 2010
Ro 48-5033	60	CHO	Treiber et al., 2007
S8921G	1.93	HEK293	Sakamoto et al., 2008
Sirolimus	+	HEK293	Oswald et al., 2010

TABLE 2
Continued

Substrate	K_m	Expression System	Reference
	μM		
Troglitazone sulfate	+	XO	Nozawa et al., 2004
YM785	+	HEK293	Umehara et al., 2008
Fluorescent in vitro OATP1B1 probe substrates			
8-Fluorescein cAMP	2.9	CHO	Bednarczyk, 2010
CDCA-NBD	1.45	HepG2	Yamaguchi et al., 2006
CGamF	+	CHO	Annaert et al., 2010
CLF	+	CHO	de Waart et al., 2010
Fluorescein-methotrexate	3.8	CHO	Gui et al., 2010
Toxins			
Arsenate	+	HEK293	Lu et al., 2006
Arsenite	+	HEK293	Lu et al., 2006
BDE47	0.31	CHO	Pacyniak et al., 2010
BDE99	0.91	CHO	Pacyniak et al., 2010
BDE153	1.91	CHO	Pacyniak et al., 2010
Demethylphalloidin	17	XO	Meier-Abt et al., 2004
Microcystin-LR	7	XO	Fischer et al., 2005
Phalloidin	39	HEK293	Fehrenbach et al., 2003
	+	XO	Herraez et al., 2009

ACU154, 0-glucuronide of PKI116 (a tyrosine kinase inhibitor); BQ-123, cyclic-pentapeptide (cyclo[D-Trp-D-Asp-L-Pro-D-Val-L-Leu]); Bamet-R2, bile acid-cisplatin derivative [*cis*-diammine-chloro-cholylglycinate-platinum(II)]; Bamet-UD2, bile acid-cisplatin derivative [cis-diammine-bisursodeoxycholate-platinum(II)]; BDE47, 2,2′,4,4′-tetrabromodiphenyl ether; BDE99, 2,2′,4,4′,5-pentabromodiphenyl ether; BDE153, 2,2′,4,4′,5,5′-hexabromodiphenylether; CDCA-NBD, chenodeoxychilyl-(Nepsilon-NBD)-lysine; CGamF, cholyl-glycylamido-fluorescein; CLF, cholyl-L-lysyl-fluorescein; CHO, Chinese hamster ovary; DADLE, [D-Ala^2,D-Leu^5]-enkephalin (opioid peptide analog); DPDPE, [D-penicillamine^{2,5}]enkephalin (opioid-receptor antagonist); EE2S, 17α-ethinylestradiol sulfate; Gd-EOB-DTPA, gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid; HEK293, human embryonic kidney 293 cells; MDCKII, Madin-Darby canine kidney cells; Ro 48-5033, active metabolite of the endothelin antagonist bosentan; S8921G, active metabolite of the SLC10A2 inhibitor S8921; SN-38, active metabolite of the anticancer drug irinotecan; XO, *Xenopus laevis* oocyte; YM785, an If channel inhibitor; +, substrate of OATP1B1, but K_m not available.

use are substrates of OATP1B1 (Brown et al., 2001; Nakai et al., 2001; Sasaki et al., 2002; Hirano et al., 2004; Schneck et al., 2004; Simonson et al., 2004; Kameyama et al., 2005; Kopplow et al., 2005; Ho et al., 2006; Noé et al., 2007; Deng et al., 2008a; Kitamura et al., 2008; Furihata et al., 2009; Niemi, 2010). However, as with many other OATP1B1 substrates, many statins are also substrates of other hepatic OATPs. For example, fluvastatin and rosuvastatin are also substrates of OATP1B3 and OATP2B1 (Kopplow et al., 2005; Ho et al., 2006; Kitamura et al., 2008), pravastatin and atorvastatin are substrates of OATP2B1 (Kobayashi et al., 2003; Grube et al., 2006), and pitavastatin is a substrate of OATP1B3 (Fujino et al., 2005).

Other drugs used in the treatment of cardiovascular diseases identified as OATP1B1 substrates include the angiotensin-converting enzyme inhibitors enalapril and temocapril, the angiotensin II receptor antagonists olmesartan and valsartan, the diuretic torsemide, and the endothelin receptor antagonists atrasentan and bosentan (Katz et al., 2006; Liu et al., 2006; Maeda et al., 2006a; Nakagomi-Hagihara et al., 2006; Yamashiro et al., 2006; Treiber et al., 2007; Yamada et al., 2007; Poirier et al., 2009; Werner et al., 2010). The angiotensin II receptor antagonists olmesartan and valsartan are also substrates of OATP1B3 (Nakagomi-Hagihara et al., 2006; Yamashiro et al., 2006), whereas telmisartan seems to be a selective substrate of OATP1B3 (Ishiguro et al., 2006). Atrasentan and bosentan are also OATP1B3 substrates (Katz et al., 2006; Treiber et al., 2007).

A number of anti-infective agents have also been identified as OATP1B1 substrates. For example, the antibiotics rifampin and benzylpenicillin, as well as certain cephalosporins, are OATP1B1 substrates (Tamai et al., 2001; Vavricka et al., 2002; Tirona et al., 2003; Nakakariya et al., 2008). Rifampin is also a substrate of OATP1B3 and benzylpenicillin is a substrate of OATP2B1 (Tamai et al., 2001; Vavricka et al., 2002). In addition, certain HIV protease inhibitors, but not non-nucleoside reverse transcriptase inhibitors, are OATP1B1 substrates (Hartkoorn et al., 2010). Moreover, the antifungal drug caspofungin is an OATP1B1 substrate (Sandhu et al., 2005).

Finally, certain anticancer agents, such as gimatecan and 7-ethyl-10-hydroxy-camptothecin (SN-38), the active metabolite of irinotecan; anti-inflammatory drugs, such as methotrexate, sirolimus, and mycophenolic acid-O-glucuronide; and the antihistamine fexofenadine are OATP1B1 substrates (Abe et al., 2001; Nozawa et al., 2005; Matsushima et al., 2008; Oostendorp et al., 2009; Oswald et al., 2010; Picard et al., 2010). SN-38, methotrexate, sirolimus, and mycophenolic acid-*O*-glucuronide are also OATP1B3 substrates, and fexofenadine is a substrate of OATP1B3 and possibly of OATP2B1 (Abe et al., 2001; Yamaguchi et al., 2008; Oswald et al., 2010; Picard et al., 2010). König et al. (2010) found the acyl glucuronide conjugate of mycophenolic acid to be an OATP1B1 substrate. Furthermore, certain diagnostic markers, such as the magnetic resonance imaging contrast agent gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid and the liver function marker bromosulfophthalein are OATP1B1 substrates (Cui et al., 2001; Kullak-Ublick et al., 2001; Kopplow et al., 2005; van der Deure et al., 2008; Leonhardt et al., 2010). Gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid is also a substrate of OATP1B3, and bromosulfophthalein is a substrate of both OATP1B3 and OATP2B1 (König et al., 2000a; Kullak-Ublick et al., 2001; Leonhardt et al., 2010).

C. Other Compounds

The need for a rapid method for screening compounds for potential inhibitory effect on OATP1B1 has driven the development of fluorescent marker substrates. Successfully developed fluorescent OATP1B1 marker substrates include fluorescently labeled cAMP, chenodeoxycholic acid, cholic acid derivates, and methotrexate (Yamaguchi et al., 2006; Annaert et al., 2010; Bednarczyk, 2010; de Waart et al., 2010; Gui et al., 2010). Several compounds showing liver toxicity have been identified as OATP1B1 substrates, suggesting that OATP1B1 may play a role in their hepatotoxic effects. For example, certain toxic flame retardants, the major phallotoxin of the mushroom *Amanita phalloides*, arsenic, as well as microcystin LR, a freshwater cyanobacterial toxin, are substrates of OATP1B1 (Fehrenbach et al., 2003; Meier-Abt et al., 2004; Fischer et al., 2005; Lu et al., 2006; Herraez et al., 2009; Pacyniak et al., 2010) (Table 2).

IV. Factors Affecting Organic Anion-Transporting Polypeptide 1B1 Activity

A. Pharmacogenetics

1. SLCO1B1 *Variants and Functional Studies.* A large number of sequence variants have been found in the *SLCO1B1* gene. The 41 identified nonsynonymous variants are described in Table 3 and Fig. 2. The first systematic investigation of *SLCO1B1* variants identified 14 nonsynonymous single-nucleotide polymorphisms (SNPs) in 15 haplotypes, many of which (coding DNA c.217T>C,

TABLE 3

Nonsynonymous sequence variations in the SLCO1B1 gene

The variant allele frequencies are given for each major population as the range of values from the dbSNP database and the articles by Iida et al. (2001); Tirona et al. (2001); Michalski et al. (2002); Nozawa et al. (2002); Nishizato et al. (2003); Morimoto et al. (2004); Niemi et al. (2004); Chung et al. (2005); Lee et al. (2005); Thompson et al. (2005); Pasanen et al. (2006a,2008b); Jada et al. (2007); Ho et al. (2008); SEARCH Collaborative Group (2008); Mwinyi et al. (2008); Seithel et al. (2008); and Man et al. (2010). Functional data in vitro are from Tirona et al. (2001, 2003); Michalski et al. (2002); Nozawa et al. (2002, 2005); Iwai et al. (2004); Kameyama et al. (2005); Ho et al. (2006); Katz et al. (2006); Tsuda-Tsukimoto et al. (2006); and Seithel et al. (2008), and in vivo from Nishizato et al. (2003); Mwinyi et al. (2004); Niemi et al. (2004); Chung et al. (2005); Lee et al. (2005); Maeda et al. (2006a); and Kalliokoski et al. (2008b) (more references in Table 5).

Location (Exon)	rs Number	Nucleotide Change	Amino Acid Change	Variant Allele Frequency			Function	
				Europeans	Sub-Saharan Africans/African Americans	East Asians	In Vitro	In Vivo
					%			
1	rs11557087	c.28A>G	p.T10A	N.A.	N.A.	N.A.	N.A.	N.A.
2	rs61760183	c.170G>A	p.R57Q	N.A.	N.A.	N.A.	N.A.	N.A.
2	rs56101265	c.217T>C	p.F73L	0–2	0	0	↓	N.A.
3	rs56061388	c.245T>C	p.V82A	0–2	0	0	↓	N.A.
4	rs2306283	c.388A>G	p.N130D	30–45	72–83	59–86	↓↔	↔
4	rs2306282	c.452A>G	p.N151S	0–3	0–2	0–4	N.A.	N.A.
4	N.A.	c.455G>A	p.R152K	N.A.	N.A.	N.A.	N.A.	N.A.
4	rs11045819	c.463C>A	p.P155T	13–23	2–10	0–3	↔	↔
4	rs72559745	c.467A>G	p.E156G	0–2	0	0	↓	N.A.
5	rs4149056	c.521T>C	p.V174A	8–20	1–8	8–16	↓	↓
5	rs72559746	c.578T>G	p.L193R	<0.3	N.A.	N.A.	↓	N.A.
5	rs4603354	c.608G>A	p.G203E	N.A.	N.A.	N.A.	N.A.	N.A.
6	N.A.	c.633A>G	p.I211M	N.A.	N.A.	0–0.5	N.A.	N.A.
6	rs79135870	c.664A>G	p.I222V	0	1	0	N.A.	N.A.
6	N.A.	c.721G>A	p.D241N	N.A.	N.A.	N.A.	N.A.	N.A.
7	rs11045852	c.733A>G	p.I245V	0	0–7	0	N.A.	N.A.
7	rs11045853	c.758G>A	p.R253Q	N.A.	N.A.	N.A.	N.A.	N.A.
7	rs72559742	c.841C>A	p.Q281K	N.A.	N.A.	N.A.	N.A.	N.A.
7	N.A.	c.875C>T	p.A292V	N.A.	N.A.	0–0.5	N.A.	N.A.
8	rs77871475	c.1000A>T	p.T334S	1	N.A.	N.A.	N.A.	N.A.
8	rs72559747	c.1007C>G	p.P336R	0	N.A.	1	↔	N.A.
8	rs61760245	c.1012T>G/A	p.Y338D/N	N.A.	N.A.	N.A.	N.A.	N.A.
8	rs79109623	c.1034C>T	p.T345M	1	N.A.	N.A.	N.A.	N.A.
8	rs55901008	c.1058T>C	p.I353T	0–2	0	0	↓	N.A.
9	rs59113707	c.1200C>G	p.F400L	0	2	0	N.A.	N.A.
9	rs77468276	c.1246G>C	p.V416L	N.A.	N.A.	N.A.	N.A.	N.A.
9	rs61176925	c.1272A>C	p.L424F	N.A.	N.A.	N.A.	N.A.	N.A.
9	rs56387224	c.1294A>G	p.N432D	0–1	0	0	↔↓	N.A.
10	rs72559748	c.1385A>G	p.D462G	0–1	0	0	↔	N.A.
10	N.A.	c.1454G>T	p.C485F	0	N.A.	1	N.A.	N.A.
10	rs59502379	c.1463G>C	p.G488A	0	3–9	0	↓	N.A.
10	rs74064213	c.1495A>G	p.I499V	N.A.	6	N.A.	N.A.	N.A.
11	rs71581987	c.1622A>T	p.Q541L	N.A.	N.A.	N.A.	N.A.	N.A.
11	rs71581988	c.1628T>G	p.L543W	0	N.A.	0–1	N.A.	N.A.
12	rs74700754	c.1724A>T	p.H575L	1	0	0	N.A.	N.A.
12	rs71581941	c.1738C>T	p.R580Stop	N.A.	N.A.	N.A.	N.A.	N.A.
13	N.A.	c.1837T>C	p.C613R	N.A.	N.A.	0–1	N.A.	N.A.
14	N.A.	c.1877T>A	p.L626Stop	N.A.	N.A.	0–1	N.A.	N.A.
14	rs34671512	c.1929A>C	p.L643F	3–9	5–13	0–1	↔	↔
14	rs56199088	c.1964A>G	p.D655G	0–2	0	0	↓	N.A.
14	rs55737008	c.2000A>G	p.E667G	0–2	0–34	0	↔	N.A.

↔, unchanged transporter function; ↓, reduced transporter activity; ↑, increased transporter activity; N.A., not available.

c.245T>C, c.467A>G, c.521T>C, c.1058T>C, c.1294A>G, c.1463G>C, c.1964A>G) conferred decreased transport activity of OATP1B1 (Tirona et al., 2001). One relatively common SNP, c.521T>C in exon 5, resulted in a decreased membrane expression of OATP1B1 and decreased transport activity toward estrone-3-sulfate and estradiol-17β-D-glucuronide. Consistent with the decreased membrane expression, the c.521T>C SNP affected mainly the maximum transport velocity compared with substrate affinity (Tirona et al., 2001). The decreased transport activity of the c.521T>C variant has been confirmed in later studies also with other substrates, such as rifampin, pravastatin, atorvastatin, rosuvastatin, atrasentan, and ezetimibe glucuronide (Tirona et al., 2003; Kameyama et al., 2005; Ho et al., 2006; Katz et al., 2006; Oswald et al., 2008).

Another common variant associated with altered transport activity of OATP1B1 is c.388A>G in exon 4. It is noteworthy that the c.388A>G and c.521T>C form four distinct haplotypes, known as **1A* (c.388A-c.521T), **1B* (c.388G-c.521T), **5* (c.388A-c.521C), and **15* (c.388G-c.521C) (Nishizato et al., 2003; Pasanen et al., 2008b). Studies on the functional consequences of the **1B* haplotype have yielded partially controversial results, some studies finding decreased activity (Michalski et al., 2002; Tirona et al., 2003; Oswald et al., 2008), some finding increased activity (Michalski et al., 2002; Kameyama et al., 2005), and many finding no change in transport activity (Tirona et al., 2001; Michalski et al., 2002; Nozawa et al., 2002, 2005; Iwai et al., 2004; Kameyama et al., 2005; Ho et al., 2006; Katz et al., 2006). These contradictory findings may be explained in part by a substrate-specific effect of the variant and/or the use of different expression systems or experimental conditions. The **15* haplotype has been consistently associated with decreased transport activity (Iwai et al., 2004; Kameyama et al., 2005; Nozawa et al., 2005; Ho et al., 2006; Katz et al., 2006; Tsuda-Tsukimoto et al., 2006; Deng et al., 2008a).

The c.578T>G SNP has been found in only one liver sample from a white person but is associated with impaired membrane expression of OATP1B1 (Michalski et al., 2002). The c.1877T>A SNP, leading to a stop codon, has been found in two chromosomes only in persons of Chinese descent (Ho et al., 2008), whereas the c.1738C>T SNP, also causing a premature stop codon, is found only in the dbSNP database (http://www.ncbi.nlm.nih.gov/projects/SNP/).

One SNP located in the promoter region of *SLCO1B1*, g.−11187G>A, which is in linkage disequilibrium with c.521T>C (Niemi et al., 2004), was not associated with SLCO1B1 mRNA expression in liver samples from patients of Japanese descent (Furihata et al., 2007). Another study investigating SLCO1B1 mRNA expression in 102 liver samples from patients of Japanese descent identified five SNPs by sequencing 1 kb upstream of exon −1, but none of the SNPs was associated with SLCO1B1 expression (Aoki et al., 2009).

In addition to variants in the *SLCO1B1* gene, variants in regulatory protein coding genes may also affect *SLCO1B1* expression. In one study, a SNP variant of the first nucleotide upstream of the translation initiation site of *NR1H4* encoding FXR (c.−1G>T), was associated with decreased mRNA expression of *SLCO1B1* (Marzolini et al., 2007).

2. Population Genetics. *SLCO1B1* variants show marked differences in their frequencies between major geographical regions (Table 3, Fig. 4). The frequencies of 12 SNPs in *SLCO1B1*, including 5 nonsynonymous variants and two promoter variants, were investigated in 941 persons from 52 populations comprising Africa, the Middle East, Asia, Europe, Oceania, and the Americas (Amerindians) (Pasanen et al., 2008b). In general, genetic differences between populations correlated well with the geographical distances considering likely routes of migration of humans out of Africa. On the other hand, the functionally significant **1B* and **15* haplotypes correlated significantly with the latitude in the northern hemisphere. In particular, **1B* showed the highest frequencies in populations near the equator, whereas the frequency of **15* increased toward north (Pasanen et al., 2008b). The reasons for the correlations are not completely understood, but the data suggest that natural selection may have shaped the global distribu-

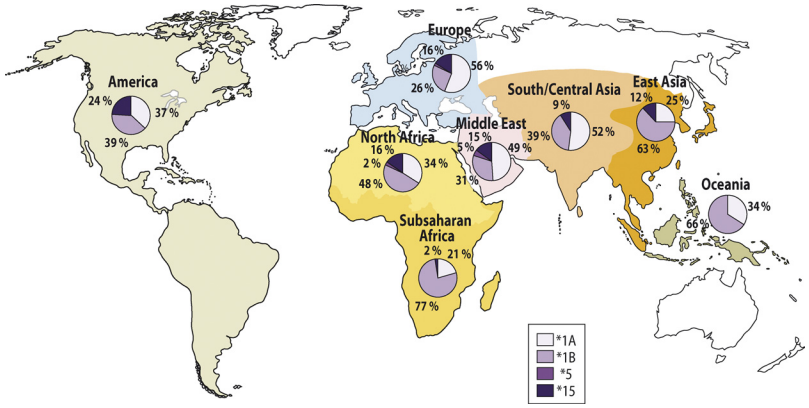

FIG. 4. Global distribution of *SLCO1B1*1A* (c.388A-c.521T), **1B* (c.388G-c.521T), **5* (c.388A-c.521C), and **15* (c.388G-c.521C) haplotypes. The data are from Pasanen et al. (2008b).

tion of *SLCO1B1* variants. The low-activity haplotypes **5* and **15* have a combined frequency of approximately 15 to 20% in Europeans, 10 to 15% in Asians, and 2% in sub-Saharan Africans (Fig. 4). The **1B* haplotype, which mostly confers increased OATP1B1 activity, has a frequency of approximately 26% in Europeans, 39% in South/Central Asians, 63% in East Asians, and as high as 77% in sub-Saharan Africans. Most of the rare functional variants of *SLCO1B1* have been found in single populations only (Table 3). The *NR1H4* c.-1G>T SNP, associated with *SLCO1B1* expression, shows an allele frequency of 2.5% in Europeans, 3.2% in Africans, and 12.1% in Chinese (Marzolini et al., 2007).

3. Effects on Drug Disposition In Vivo. The pharmacokinetic effects of *SLCO1B1* variants have been investigated for more than 20 clinically used drugs (Table 4). The first compound investigated was pravastatin. In the first published study, the pharmacokinetics of pravastatin after a single 10-mg oral dose was investigated in 23 healthy Japanese volunteers with different *SLCO1B1* genotypes (Nishizato et al., 2003). A significantly reduced nonrenal clearance was observed in persons with the *SLCO1B1*1B/*15* genotype compared with those with the **1B/*1B* genotype (Nishizato et al., 2003), consistent with a reduced hepatic uptake in association with the **15* haplotype. In another study, the coding and flanking regions of the *SLCO1B1* gene were sequenced in 41 healthy white volunteers with single-dose pharmacokinetic data for 40 mg of pravastatin (Niemi et al., 2004). In that study, individuals carrying the c.521T>C variant (i.e., **5* of **15* haplotype) showed an increased area under the plasma concentration-time curve (AUC) of pravastatin, similarly consistent with a reduced hepatic uptake. Moreover, a SNP in the promoter region, g.−11187G>A, was associated with increased AUC of pravastatin, but this was most likely due to linkage disequilibrium between the promoter variant and c.521T>C (Niemi et al., 2004). None of the other variants found had an effect on pravastatin pharmacokinetics. In a later study, the effects of the *SLCO1B1* c.521T>C variant were investigated on the pharmacokinetics of pravastatin during multiple dosing (Igel et al., 2006), confirming that the effect can be seen also at steady state.

In a series of genotype-panel studies, the effects of the *SLCO1B1* c.521T>C SNP were investigated on the pharmacokinetics of fluvastatin, pravastatin, simvastatin, atorvastatin, and rosuvastatin in the same 32 healthy young subjects, allowing direct comparisons between statins (Niemi et al., 2006b; Pasanen et al., 2006b, 2007) (Fig. 5). It is noteworthy that the largest effect was seen on simvastatin acid, the active form of simvastatin (3.2-fold increased mean AUC in c.521CC homozygotes). The *SLCO1B1* genotype had a marked effect also on atorvastatin, a slightly smaller effect on pravastatin and rosuvastatin but had no significant effect on fluvastatin. These differences between the statins may be partly explained by varying contributions of other influx transporters to their hepatic uptake, as well as their different physicochemical and pharmacokinetic properties. Based on these findings and on the concentration-dependent skeletal muscle toxicity of statins, it could be predicted that the low activity *SLCO1B1* variants (i.e., **5* and **15* haplotypes) are associated with an increased risk of statin-induced myopathy (Pasanen et al., 2006b). The risk could be predicted to be largest for simvastatin, followed by atorvastatin, pravastatin, and rosuvastatin. The *SLCO1B1* c.521T>C genotype has been shown to have a marked effect also on the pharmacokinetics of pitavastatin (Chung et al., 2005; Ieiri et al., 2007; Deng et al., 2008a).

In contrast to the effects of the *SLCO1B1* c.521T>C SNP, the **1B* haplotype (c.388G-c.521T) has been associated with a decreased AUC of pravastatin (Mwinyi et al., 2004; Maeda et al., 2006a). The AUC of 10 mg of pravastatin was 35% lower in healthy Japanese persons with the *SLCO1B1*1B/*1B* genotype than in those with the **1A/*1A* genotype (Maeda et al., 2006a), consistent with an enhanced hepatic uptake in association with the **1B* haplotype. On the other hand, the pharmacokinetics of rosuvastatin do not seem to be affected by the *SLCO1B1*1B* haplotype (Lee et al., 2005; Choi et al., 2008), suggesting that the effects of this variant may be substrate specific.

In one study, the *SLCO1B1* c.521CC genotype, compared with the c.521TT genotype, was found to be associated with nearly a 3-fold increase in AUC for repaglinide, a short-acting meglitinide analog antidiabetic drug, in 56 healthy white volunteers (Niemi et al., 2005a). Repaglinide has not been identified as an OATP1B1 substrate in vitro, but the plasma concentrations of repaglinide are markedly increased by the OATP1B1 inhibitors cyclosporine (also a CYP3A4 inhibitor) and gemfibrozil (also a CYP2C8 inhibitor) (Niemi et al., 2003c; Kajosaari et al., 2005b), and repaglinide has been shown to inhibit OATP1B1 in vitro (Bachmakov et al., 2008). The effect of the *SLCO1B1* c.521T>C SNP on repaglinide pharmacokinetics has been confirmed in later studies and found to be consistent throughout a wide dose range (Kalliokoski et al., 2008c,d). Moreover, the *SLCO1B1*1B/*1B* genotype has been associated with a 32% decrease in AUC for repaglinide compared with the **1A/*1A* genotype (Kalliokoski et al., 2008b). Despite the lack of direct in vitro evidence, the data strongly suggest that OATP1B1 mediates the hepatic uptake of repaglinide.

In healthy Chinese volunteers, the AUC of nateglinide, another meglitinide analog antidiabetic, was found to be increased approximately 2-fold in persons with the c.521CC genotype ($n = 2$) and 1.8-fold in those with the c.521TC genotype ($n = 4$) compared with the c.521TT genotype (Zhang et al., 2006). Larger genotype panel studies in healthy Caucasian volunteers did not confirm the effects of *SLCO1B1* genotype (either c.521T>C SNP or **1B* haplotype) on nateglinide pharmacokinetics (Kalliokoski et al.,

TABLE 4
Effects of genetic variability in SLCO1B1 on the pharmacokinetics of drugs

Drug	Dose	*n*	Ethnicity	Effect	Reference
Atorvastatin	20 mg	32	White	c.521CC vs. **1A/*1A*: AUC 144% ↑, 2-OH-atorvastatin AUC 100% ↑ c.521CC vs. c.521TC: AUC 61% ↑	Pasanen et al., 2007
Atorvastatin	20 mg	28	Korean	**15/*15* vs. **1A/*1A*, **1A/*1B* or **1B/*1B*: AUC 124% ↑, 2-OH-atorvastatin AUC ↑ **15/*15* vs. **1A/*15*, **1B/*15*: AUC 84% ↑	Lee et al., 2010
Atrasentan	10 mg	44 (single dose) 38 (steady state)	Mixed	Poor vs. extensive activity genotype[a]: single dose AUC 73% ↑ Intermediate vs. extensive activity genotype: single dose AUC 14% ↑, steady-state AUC 27% ↑ (no poor activity genotypes in steady state)	Katz et al., 2006
Cyclosporine	3 mg/kg i.v. and 10 mg/kg p.o.	104 renal transplant recipient children	White	c.521T>C: N.S.	Fanta et al., 2008
Ezetimibe	20 mg	35	White	**1B/*1B* vs. **1A/*1A*: 51% ↓ **1A/*1B* vs. **1A/*1A*: 21% ↓	Oswald et al., 2008
Fexofenadine	180 mg	20	White	c.521CC vs. c.521TT: AUC 127% ↑ c.521CC vs. c.521TC: AUC 76% ↑	Niemi et al., 2005d
Fluvastatin	40 mg	32	White	c.521T>C: N.S.	Niemi et al., 2006b
Irinotecan	100 mg/m^2 or 375 mg/m^2	71 cancer patients	Asian	**15/*15* or **1B/*15* vs. **1A/*1B* or **1B/*1B*: CL 52% ↓, SN-38G C_{max} 65% ↓, AUC 45% ↓ **15/*15* or **1B/*15* vs. **1A/*1A*: C_{max} 83% ↑, AUC 127% ↑, CL 67% ↓, SN-38 C_{max} 130% ↑, AUC 86% ↑, SN-38G C_{max} 81% ↓, AUC 70% ↓	Xiang et al., 2006
Irinotecan	80 mg/m^2 and cisplatin 60 mg/m^2	81 cancer patients	Korean	g.−11187AA vs. g.−11187GA or g.−11187GG: SN-38 AUC 113% ↑ c.521CC or c.521TC vs. c.521TT: SN-38 AUC 29% ↑	Han et al., 2008
Irinotecan	80 or 65 mg/m^2	107 cancer patients	Korean	c.521CC or c.521TC vs. c.521TT: SN-38 AUC 26% ↑	Han et al., 2009
Irinotecan	300 or 350 mg/m^2	85 cancer patients		c.521CC or c.521TC vs. c.521TT: irinotecan AUC 19% ↑	Innocenti et al., 2009
Irinotecan	100, 150, or 60 mg/m^2 with 60 mg/m^2 cisplatin; 70 mg/m^2 with 80 mg/m^2 cisplatin	117 cancer patients	Japanese	c.521CC or c.521TC vs. c.521TT: SN-38 AUC ↑	Sai et al., 2010
Lopinavir	variable, with 200 mg of ritonavir	148 HIV patients	White	c.521CC vs. c.521TT: CL 21% ↓ c.521TC vs. c.521TT: CL 14% ↓ rs4149032 homozygotes vs. noncarriers: CL 29% ↑ rs4149032 homozygotes vs. heterozygotes: CL 21% ↑ c.463AA vs. c.463CC: CL 116% ↑ c.463AA vs. c.463CA: CL 104% ↑	Lubomirov et al., 2010
Lopinavir	variable, with ritonavir	99 HIV patients	Mixed	c.521CC vs. c.521TT: C_{trough} 49% ↑ c.521CC vs. c.521TC: C_{trough} 16% ↑	Kohlrausch et al., 2010
Lopinavir	400 mg, with 100 mg of ritonavir b.i.d.	349 HIV patients	Unknown	c.521CC vs. c.521TT: C_{min} and C_{2-6} ↑ c.521CC vs. c.521TC: C_{min} and C_{2-6} ↑ c.521TC vs. c.521TT: C_{min} and C_{2-6} ↑	Hartkoorn et al., 2010
Methotrexate	2–5 g/m^2	434 + 206 children with ALL	Mixed	rs4149081/rs11045879: 6–14 ml/min/m^2 ↑ CL per variant allele c.521T>C: 4–14 ml/min/m^2 ↓ CL per C-allele	Treviño et al., 2009
Mycophenolic acid	0.75–1 g b.i.d. with tacrolimus	87 renal transplant recipients	Japanese	c.388A>G or c.521T>C: N.S.	Miura et al., 2007
Mycophenolic acid	0.5–1 g b.i.d. with tacrolimus	80 renal transplant recipients	Japanese	c.521TC or c.521CC vs. c.521TT: mycophenolic acid glucuronide AUC 27% ↓	Miura et al., 2008
Nateglinide	90 mg	17	Chinese	c.521CC vs. c.521TT: AUC 108% ↑ c.521TC vs. c.521TT: AUC 82% ↑	Zhang et al., 2006

TABLE 4
Continued

Drug	Dose	*n*	Ethnicity	Effect	Reference
Nateglinide	60 mg	24	White	*1B/*1B vs. *1A/*1A: N.S.	Kalliokoski et al., 2008b
Nateglinide	60 mg	32	White	c.521CC or c.521TC vs. *1A/*1A: N.S.	Kalliokoski et al., 2008c
Olmesartan	10 mg	10	Japanese	*15/*15 vs. *1B/*1B: CL_{oral} ↓	Suwannakul et al., 2008
Pioglitazone	15 mg	32	White	c.521T>C: N.S.	Kalliokoski et al., 2008e
Pitavastatin	1–8 mg	24	Korean	c.521TC vs. *1B/*1B: dose-normalized AUC 76% ↑, C_{max} 123% ↑, $t_{1/2}$ 30% ↑ c.521TC vs. *1A/*1B or *1B/*1B: dose-normalized AUC 25% ↑, C_{max} 62% ↑	Chung et al., 2005
Pitavastatin	2 mg	38	Japanese	c.521TC vs. *1B/*1B: AUC 76% ↑ *15/*15 vs. *1B/*1B: AUC 208% ↑ *15/*15 vs. *1B/*15: AUC 74% ↑	Ieiri et al., 2007
Pitavastatin	4 mg	11	Korean	*15/*15 vs. *1A/*1A: AUC 162% ↑	Deng et al., 2008b
Pitavastatin	2 mg	15	Chinese	c.388GG or c.388AG vs. c.388AA: AUC 46% ↓, C_{max} 42% ↓	Wen and Xiong, 2010
Pravastatin	10 mg	23	Japanese	*1B/*15 vs. *1B/*1B: CL_{nr} 45% ↓	Nishizato et al., 2003
Pravastatin	40 mg	30	White	c.521TC vs. *1A/*1A: AUC 42% ↑ c.521TC vs. *1A/*1B or *1B/*1B: AUC 118% ↑	Mwinyi et al., 2004
Pravastatin	40 mg	41	White	g.−11187GA vs. g.−11187GG: AUC 98% ↑ c.521TC vs. c.521TT: AUC 106% ↑ *15 heterozygotes vs. non-carriers: AUC 93% ↑ g.−11187A-c.388G-c.521C heterozygotes vs. non-carriers: AUC 130% ↑	Niemi et al., 2004
Pravastatin	40 mg/day	16	White	g.−11187G-c.388G-c.521C or g.−11187A-c.388G-c.521C carriers vs. non-carriers: steady-state AUC 110% ↑	Igel et al., 2006
Pravastatin	10 mg	23	Japanese	*1B/*1B vs. *1A/*1A: AUC 35% ↓ *1B/*15 vs. *1A/*15: AUC 45% ↓	Maeda et al., 2006a
Pravastatin	40 mg	32	White	c.521CC vs. *1A/*1A: AUC 91% ↑, male 232% ↑ c.521CC vs. c.521 TC: AUC 74% ↑, male 102% ↑	Niemi et al., 2006b
Pravastatin	40 mg	107	Mixed	*1A/*15 vs. *1A/*1A: AUC 45% ↑ *1A/*15 vs. *1B/*1B: AUC 80% ↑ *15/*15 vs. *1A/*1A: AUC 92% ↑ *15/*15 vs. *1B/*1B: AUC 149% ↑	Ho et al., 2007
Pravastatin	40 mg	11	Korean	*15/*15 vs. *1A/*1A: AUC 99% ↑	Deng et al., 2008b
Repaglinide	0.25 mg	56	White	c.521CC vs. c.521TT: AUC 188% ↑ c.521CC vs. c.521TC: AUC 107% ↑	Niemi et al., 2005b
Repaglinide	0.5 mg	32	White	c.521CC vs. *1A/*1A: AUC 72% ↑, M2 AUC 112% ↑, M4 AUC 81% ↑	Kalliokoski et al., 2008c
Repaglinide	0.5 mg	24	White	*1B/*1B vs. *1A/*1A: AUC 32% ↓	Kalliokoski et al., 2008b
Repaglinide	0.25 mg 0.5 mg 1 mg 2 mg	20	White	c.521CC vs. *1A/*1A: AUC 82% ↑ c.521CC vs. *1A/*1A: AUC 72% ↑ c.521CC vs. *1A/*1A: AUC 56% ↑ c.521CC vs. *1A/*1A: AUC 108% ↑	Kalliokoski et al., 2008d
Rifampin	450 or 600 mg	72 patients with pulmonary tuberculosis + 16 healthy volunteers	Mixed	c.463CA vs. c.463CC: AUC 42% ↓	Weiner et al., 2010
Rosiglitazone	4 mg	32	White	c.521T>C: N.S.	Kalliokoski et al., 2008e
Rosuvastatin	40 mg	36	White	*15/*15 vs. *1A/*1A: AUC 117% ↑ *15/*15 vs. *1A/*1B: AUC 108% ↑	Lee et al., 2005
		36	Chinese	N.S. (no c.521CC included)	
		35	Malay	N.S. (no c.521CC included)	
		35	Asian-Indian	N.S. (no c.521CC included)	
Rosuvastatin	10 mg	32	White	c.521CC vs. *1A/*1A: AUC 65% ↑	Pasanen et al., 2007
Rosuvastatin	10 mg	30	Korean	*15/*15 vs. *1A/*1A: AUC 119% ↑ *1A/*15 vs. *1A/*1A: AUC 91% ↑ *15/*15 vs. *1A/*15: AUC 82% ↑	Choi et al., 2008
Simvastatin	40 mg	32	White	c.521CC vs. *1A/*1A: simvastatin acid AUC 221% ↑ c.521CC vs. c.521TC: simvastatin acid AUC 162% ↑	Pasanen et al., 2006b

TABLE 4
Continued

Drug	Dose	*n*	Ethnicity	Effect	Reference
Temocapril	2 mg	23	Japanese	N.S.	Maeda et al., 2006a
Torsemide	10 mg	99	White	**1B/*1B* vs. **1A/*1A*: CL_{nr} 40% ↑ **5/*5* vs. **1A/*1A*: CL_{nr} 68% ↓ **15/*15* vs. **1A/*1A*: CL_{nr} 35% ↓	Vormfelde et al., 2008
Torsemide	10 mg/day	24	White	c.521TC vs. c.521TT: AUC 38% ↑	Werner et al., 2008
Torsemide	10–20 mg/day	90 patients	White	c.521CC or c.521TC vs. c.521TT: AUC ↑	Werner et al., 2010
Valsartan	40 mg	23	Japanese	N.S.	Maeda et al., 2006a

**1A*, c.388A-c.521T; **1B*, c.388G-c.521T; **5*, c.388A-c.521C; **15*, c.388G-c.521C; ALL, acute lymphoblastic leukemia; AUC, area under the plasma concentration-time curve; CL, clearance; CL_{nr}, non-renal clearance.

[a] Extensive activity genotype is defined as homozygosity for high-activity haplotype (c.521T-c.1463G), intermediate activity as heterozygosity for low-activity haplotype (c.521C-c.1463G, c.521T-c.1463C, c.521C-c.1463C), and poor activity as homozygosity or compound heterozygosity for low-activity haplotype.

2008b,c). The thiazolidinedione antidiabetic drugs rosiglitazone and pioglitazone inhibit OATP1B1 in vitro (Nozawa et al., 2004; Bachmakov et al., 2008), have been identified as potential OATP1B1 substrates in silico (Chang et al., 2005), and interact with the OATP1B1 inhibitor gemfibrozil in vivo (Niemi et al., 2003b; Jaakkola et al., 2005). However, gemfibrozil, or more specifically its glucuronide metabolite, is also a potent inhibitor of CYP2C8 in vivo (Backman et al., 2002; Niemi et al., 2003c; Shitara et al., 2004; Ogilvie et al., 2006), which could explain the effects. Furthermore, the *SLCO1B1* c.521T>C SNP has no effect on the pharmacokinetics of either rosiglitazone or pioglitazone, or their metabolites (Kalliokoski et al., 2008e; Aquilante et al., 2008), indicating that OATP1B1-mediated hepatic uptake is not rate-determining in the pharmacokinetics of these drugs in vivo. A single intravenous dose of the OATP1B inhibitor rifampin has decreased the hepatic uptake of glyburide (International Nonproprietary Name, glibenclamide) (Zheng et al., 2009), but it is not known whether any sulfonylurea antidiabetic drug is a substrate of OATP1B1 and the possible effects of *SLCO1B1* polymorphism on sulfonylureas remain to be investigated (Kalliokoski et al., 2010).

In a genome-wide association study with 434 children with acute lymphoblastic leukemia, two *SLCO1B1* SNPs, rs11045879 and rs4149081, were associated with an increased clearance of methotrexate (Treviño et al., 2009), consistent with an increased hepatic uptake in association with these variants. These associations were validated in a cohort of an additional 206 children. The rs11045879 and rs4149081 SNPs were in a complete linkage disequilibrium with each other and also showed a significant correlation with the c.521T>C SNP ($r^2 > 0.84$), which was not included in the genome-wide genotyping. The c.521T>C SNP was genotyped in a subset of the patients and was found to be associated with a reduced clearance of methotrexate at the genome-wide significance level. No variants in other genes were associated with methotrexate clearance (Treviño et al., 2009).

In a recent study, the *SLCO1B1* c.463C>A SNP was associated with a reduced AUC of rifampin (Weiner et al., 2010). On the other hand, the c.521T>C SNP has had no effect on the induction of hepatic CYP3A4 by rifampin (Niemi et al., 2006a), suggesting that *SLCO1B1* polymorphism may affect the systemic exposure of rifampin but may have only a minor effect on its liver exposure. Likewise, the c.463C>A SNP has been associated with enhanced lipid-lowering efficacy of fluvastatin (Couvert et al., 2008). The c.463C>A SNP has had no effect on transporting activity of OATP1B1 in in vitro studies (Tirona et al., 2001), and the associations may be caused by the strong linkage disequilibrium between the c.463C>A and c.388A>G (i.e., **1B* haplotype) SNPs (Pasanen et al., 2008) and require confirmation in future studies.

In addition, the pharmacokinetics of atrasentan, ezetimibe, fexofenadine, irinotecan, lopinavir, olmesartan, and torsemide have shown associations with the *SLCO1B1* genotype (Niemi et al., 2005c; Katz et al., 2006; Xiang et al., 2006; Han et al., 2008; Oswald et al., 2008; Suwannakul et al., 2008; Vormfelde et al., 2008; Werner et al., 2008; Han et al., 2009; Innocenti et al., 2009; Hartkoorn et al., 2010; Kohlrausch et al., 2010; Lubomirov et al., 2010; Sai et al., 2010; Werner et al., 2010). In general, the *SLCO1B1* c.521T>C variant (**5* or **15* haplotype) is associated with impaired hepatic uptake and increased plasma concentrations of most OATP1B1 substrates, whereas the *SLCO1B1*1B* haplotype is associated with an enhanced hepatic uptake and decreased plasma concentrations of some OATP1B1 substrates.

4. Effects on the Disposition of Endogenous Compounds. One study investigated the effects of the *SLCO1B1* c.521T>C SNP on the effects of single-dose fluvastatin, pravastatin, simvastatin, atorvastatin, and rosuvastatin on markers of cholesterol absorption and synthesis in healthy white volunteers (Pasanen et al., 2008a). Although all statins decreased the plasma lathosterol-to-cholesterol ratio, a marker of cholesterol synthesis rate, no differences were seen in the responses between the *SLCO1B1* genotypes. It is noteworthy that persons with the c.521CC genotype had a 40% higher fasting plasma desmosterol-to-cholesterol ratio than those with the **1A/*1A* genotype, indicating an increased baseline cholesterol synthesis rate in association with impaired OATP1B1 activity (Pasanen et al., 2008a). This led to a hypothesis that genetically im-

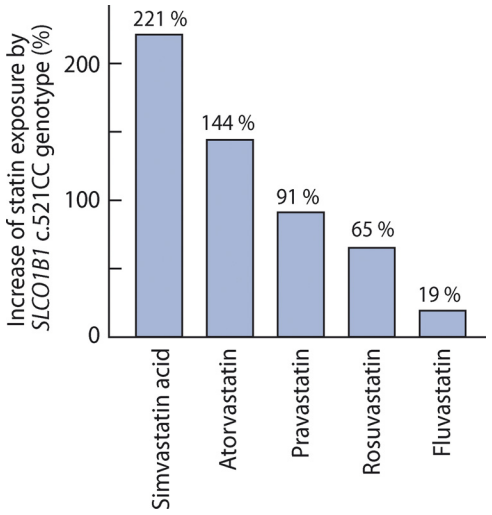

FIG. 5. Effects of the *SLCO1B1* c.521T>C variant on the exposure (area under the plasma statin concentration-time curve) to different statins. The data are from Niemi et al. (2006b) and Pasanen et al. (2006b, 2007).

paired OATP1B1 activity decreases the hepatic uptake of bile acids, resulting in an increased conversion of cholesterol to bile acids and thereby to an enhanced cholesterol synthesis rate. Indeed, the *SLCO1B1* genotype was later found to be associated with the plasma concentrations of certain bile acids and bile acid synthesis rate (Xiang et al., 2009). The fasting plasma concentrations of ursodeoxycholic acid, glycoursodeoxycholic acid, chenodeoxycholic acid, and glycochenodeoxycholic acid were between 50 and 240% higher in persons with the *SLCO1B1* c.521CC, c.521TC, or **1A/*1A* genotype than in those with the **1B/*1B* genotype. Moreover, the ratio of bile acid synthesis marker 7α-hydroxy-4-cholesten-3-one to cholesterol concentration in plasma was 62% higher in the **1A/*1A* participants than in the **1B/*1B* participants, indicating a reduced bile acid synthesis rate in association with the **1B* haplotype (Xiang et al., 2009). Taken together, the results suggest that OATP1B1 plays an important role in the hepatic uptake of bile acids, thereby affecting cholesterol homeostasis.

The plasma concentrations of bilirubin and its conjugates have also been associated with the *SLCO1B1* genotype (van der Deure et al., 2008; Xiang et al., 2009). Three recently published genome-wide association studies have investigated the genetic factors associated with bilirubin levels (Johnson et al., 2009; Sanna et al., 2009; Kang et al., 2010). In one of them in approximately 9500 white persons, variants in the *UGT1A1* locus showed strongest association with total serum bilirubin; the only other significant association seen was with the *SLCO1B1* c.521T>C SNP, so that those with the C allele showed an increased bilirubin concentration (Johnson et al., 2009). Another study in 4300 white persons found a strong association of a noncoding *SLCO1B3* SNP with both conjugated and unconjugated bilirubin, in addition to strong effects of *UGT1A1* and *G6PD* SNPs and moderate effects of the *SLCO1B1* c.521T>C and c.388A>G SNPs (Sanna et al., 2009). In the most recent study in approximately 1000 Koreans, only variants in the *UGT1A1* and *SLCO1B3* loci were associated with total serum bilirubin concentrations at the genome-wide significance level (Kang et al., 2010). The *SLCO1B1* c.521T>C SNP has been found to be associated with the presence of bilirubin in gallstones but not with the overall risk of gallstone formation (Buch et al., 2010).

Other endogenous compounds associated with *SLCO1B1* genotype include estrone-3-sulfate and thyroxine. In one study, the plasma concentrations of estrone-3-sulfate and thyroxine were 39 and 23% higher, respectively, in carriers of the *SLCO1B1* c.521T>C SNP than in noncarriers, whereas no association was seen with thyroid-stimulating hormone or triiodothyronine (van der Deure et al., 2008). There is evidence to suggest that OATP1B1 participates in the in vivo hepatic uptake of several endogenous compounds, but further research is needed in this field.

5. Clinical Implications. The clinical significance of *SLCO1B1* genetic polymorphism is best exemplified by its effects on statin therapy. Statins are usually very well tolerated, but they can cause myopathy as a rare, plasma concentration-dependent adverse reaction (Thompson et al., 2003; Neuvonen et al., 2006; Ghatak et al., 2010). Symptoms of statin-induced myopathy include fatigue, muscle pain, tenderness, weakness, and cramping, which can occur with or without an increase in blood creatine kinase concentration. The clinical spectrum of statin-induced myopathy ranges from a mild and relatively common myalgia (5–10% of statin users/year) to a life-threatening and rare rhabdomyolysis (0.001–0.005% of statin users/year) (Staffa et al., 2002; Graham et al., 2004). Known risk factors for statin-induced myopathy and rhabdomyolysis include a high statin dose, drug-drug interactions (especially those that raise statin plasma concentrations), very high age, existence of multiple concomitant diseases, hypothyroidism, and certain inherited muscle disorders (Thompson et al., 2003; Neuvonen et al., 2006; Ghatak et al., 2010).

Because statin-induced myopathy is a concentration-dependent adverse drug reaction, it is reasonable to expect that the *SLCO1B1* c.521T>C SNP increases the risk of myopathy during treatment with simvastatin, pitavastatin, atorvastatin, pravastatin, and rosuvastatin (Fig. 5), particularly when using them in high daily doses. This was confirmed for simvastatin in a genome-wide association study involving 85 patients with myopathy during a high-dose (80 mg/day) simvastatin therapy and 90 matched control subjects, as a part of the 12,000-patient Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine trial (SEARCH Collaborative Group, 2008). In that study, only a noncoding SNP in the *SLCO1B1* gene, which is in strong linkage disequilibrium with the c.521T>C SNP (r^2 = 0.97), was associated with simvastatin-induced myopathy. The odds ratio for myopathy was 4.5 per copy of the c.521C

allele and as high as 16.9 in CC homozygotes compared with TT homozygotes. More than 60% of the myopathy cases were attributed to the C allele. Of the patients with the CC genotype, 18.2% developed myopathy during the first 5 years of the high-dose simvastatin therapy, with most cases occurring during the first year, compared with an overall risk of 2.83% in TC heterozygotes and 0.63% in TT homozygotes (SEARCH Collaborative Group, 2008) (Fig. 6). The association was replicated in 10 000 patients on 40 mg/day simvastatin in the Heart Protection Study, yielding a relative risk of 2.6 per copy of the C allele (SEARCH Collaborative Group, 2008). The *SLCO1B1* c.521T>C SNP was recently found to be associated also with milder forms of simvastatin-, atorvastatin-, and pravastatin-induced adverse reactions, even during the use of low statin doses (Voora et al., 2009).

Because the *SLCO1B1* c.521T>C SNP markedly reduces the uptake of simvastatin acid into hepatocytes (where it inhibits cholesterol synthesis) and increases its plasma concentrations, thus enhancing the risk of myopathy particularly during high-dose simvastatin therapy (Fig. 6), it is obvious that high-dose simvastatin should be avoided in carriers of this SNP. Given that statin-induced myopathy is a concentration-dependent adverse reaction, it is advisable to also avoid high doses of atorvastatin and pitavastatin, and probably also of rosuvastatin and pravastatin, in carriers of this SNP, bearing in mind that the effect is different on different statins (Fig. 5). In individual patients, the effect of this SNP on plasma statin concentrations can be greater than the average effect seen in healthy volunteers. Thus, for example, an exposure to simvastatin acid more than 5-fold greater than usual may occur in simvastatin users, which may explain occasional occurrence of myotoxicity at relatively low doses. Particular attention should be paid to patients carrying the *SLCO1B1* variant and to using drugs that interact with certain statins, such as amiodarone or gemfibrozil (Backman et al., 2000; Neuvonen et al., 2006; Becquemont et al., 2007), because the *SLCO1B1* c.521T>C SNP and interacting drugs may have additive effects on statin pharmacokinetics. Moreover, other genetic factors, such as the *ABCG2* c.421G>A SNP, which was recently found to significantly raise the plasma concentrations of rosuvastatin, atorvastatin, and fluvastatin, but not simvastatin acid or pravastatin (Keskitalo et al., 2009a,b), might have an additive effect with the *SLCO1B1* c.521T>C SNP or interacting drugs. Because the *SLCO1B1* c.521T>C SNP has had no significant effect on the pharmacokinetics of fluvastatin, it is likely that the variant does not confer an increased risk of fluvastatin-induced myopathy (Niemi et al., 2006b).

Because the *SLCO1B1* c.521T>C SNP decreases the hepatic uptake of most statins, it has been hypothesized that it may be associated with an attenuated cholesterol-lowering response to statin therapy (Niemi et al., 2005e; Gerloff et al., 2006). In the first prospective study investigating this, the cholesterol-lowering efficacy of 40 mg/day pravastatin for 3 weeks was not different among eight healthy persons carrying the *SLCO1B1* c.521C allele and noncarriers (Igel et al., 2006). In the Heart Protection Study, the low-density lipoprotein cholesterol-lowering effect of 40 mg/day simvastatin was 1.3% smaller per copy of C allele (SEARCH Collaborative Group, 2008), consistent with reduced hepatic uptake of active simvastatin acid. Nevertheless, the balance of evidence suggests that *SLCO1B1* polymorphism does not have a clinically meaningful effect on the cholesterol-lowering efficacy of statin therapy, probably because the total hepatic exposure to statins is unlikely markedly decreased as a result of reduced OATP1B1 activity as most statins are mainly eliminated via the liver. This is also supported by physiologically based modeling of pravastatin pharmacokinetics, which indicates that variation in hepatic uptake has a major effect on the plasma exposure to pravastatin but only a small effect on liver exposure (Watanabe et al., 2009; Watanabe et al., 2010). Thus, the *SLCO1B1* c.521C allele decreases the therapeutic index of simvastatin and that of most other statins by increasing plasma statin concentra-

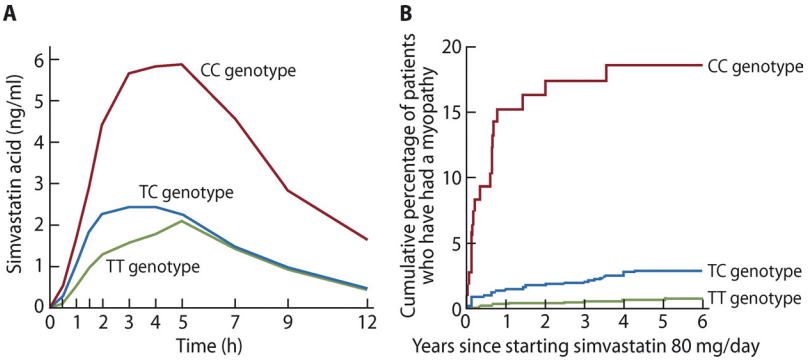

FIG. 6. Effects of the *SLCO1B1* c.521T>C variant on the plasma concentrations of active simvastatin acid after a single 40-mg dose of simvastatin in healthy volunteers, (A) and on the cumulative incidence of myopathy during treatment with 80 mg/day simvastatin (B). [A reproduced from Pasanen MK, Neuvonen M, Neuvonen PJ, and Niemi M (2006) SLCO1B1 polymorphism markedly affects the pharmacokinetics of simvastatin acid. *Pharmacogenet Genomics* **16**:873–879. Copyright © 2006 Lippincott Williams & Wilkins. Used with permission. B reproduced from SEARCH Collaborative Group, Link E, Parish S, Armitage J, Bowman L, Heath S, Matsuda F, Gut I, Lathrop M, and Collins R (2008) SLCO1B1 variants and statin-induced myopathy—a genomewide study. *N Engl J Med* **359**:789–799. Copyright © 2008 Massachusetts Medical Society. Used with permission. All rights reserved.]

TABLE 5
Inhibition of OATP1B1 by drugs and related compounds in vitro

Inhibitor	IC_{50} or K_i	Reference
	μM	
Amprenavir	12.8	Annaert et al., 2010
Atazanavir	1.5	Annaert et al., 2010
Atorvastatin	0.87	Hsiang et al., 1999; Chen et al., 2005
Atorvastatin lactone	2.6	Chen et al., 2005
Beclomethasone	6.7	Gui et al., 2010
Bezafibrate	45.2	Gui et al., 2009
Bromocriptine	0.7	Gui et al., 2010
Bromosulfophthalein	0.044–0.6	König et al., 2000b; Nakai et al., 2001; Fehrenbach et al., 2003; Fischer et al., 2005; Annaert et al., 2010; Han et al., 2010
Carbamazepine	188	Gui et al., 2008, 2009
Caspofungin	+	Sandhu et al., 2005
Chenodeoxycholic acid	3.4	Gui et al., 2009
Ciglitazone	+	Gui et al., 2009
Clarithromycin	8.26–96	Hirano et al., 2006; Seithel et al., 2007
Clotrimazole	7.6–9.0	Gui et al., 2008, 2009
Cyclosporine	0.021–2.2	Fehrenbach et al., 2003; Shitara et al., 2003; Tirona et al., 2003; Campbell et al., 2004; Simonson et al., 2004; Hirano et al., 2006; Ho et al., 2006; Treiber et al., 2007; Amundsen et al., 2010; Bednarczyk, 2010
Darunavir	3.1	Annaert et al., 2010
Digoxin	31.7	Hirano et al., 2006
Elacridar	+	Oostendorp et al., 2009
Eltrombopag	2.71	European Medicines Agency, 2010a
Erythromycin	11.4–217	Hirano et al., 2006; Seithel et al., 2007
Estradiol	3.3	Gui et al., 2009
Estropipate	0.06	Gui et al., 2010
Fenofibrate	105.2	Gui et al., 2009
Gd-EOB-DTPA	600	Leonhardt et al., 2010
Gemfibrozil	4.0–72	Schneck et al., 2004; Shitara et al., 2004; Hirano et al., 2006; Ho et al., 2006; Noé et al., 2007
Gemfibrozil-1-*O*-glucuronide	22.6–24	Shitara et al., 2004; Hirano et al., 2006
Glyburide	0.746–1.14	Hirano et al., 2006; Bednarczyk, 2010
Hyperforin	0.82	Tirona et al., 2003
Indinavir	5.84–18.4	Tirona et al., 2003; Campbell et al., 2004; Hirano et al., 2006; Annaert et al., 2010
Indocyanine green	0.112	Cui et al., 2001
Irinotecan	+	Nozawa et al., 2005
Ketoconazole	19.2	Hirano et al., 2006; Gui et al., 2009
Lovastatin	6.1	Hsiang et al., 1999; Sandhu et al., 2005; Gui et al., 2008
Lovastatin acid	4.0	Chen et al., 2005
Lovastatin lactone	12.7–28	Chen et al., 2005; Gui et al., 2009
Lopinavir	0.5	Annaert et al., 2010
Metyrapone	+	Gui et al., 2008, 2009
Miconazole	+	Gui et al., 2009
Mifepristone	2.2–3.3	Gui et al., 2008, 2009
Moricizine	8.1	Gui et al., 2010
Nelfinavir	0.93	Tirona et al., 2003
Niflumic acid	3.7	Gui et al., 2010
Paclitaxel	0.03	Gui et al., 2008, 2009
Pantoprazole	+	Oostendorp et al., 2009
Pazopanib	0.79	U.S. Food and Drug Administration, 2009
Phenytoin	+	Gui et al., 2009
Pioglitazone	+	Nozawa et al., 2004
Pravastatin	21.8	Gui et al., 2009; Hsiang et al., 1999
Ramipril	4.0	Gui et al., 2010
Repaglinide	1.1–2.2	Bachmakov et al., 2008; Gui et al., 2010
Resveratrol	11.2	Gui et al., 2010
Rifampin	0.477–17	Vavricka et al., 2002; Tirona et al., 2003; Hirano et al., 2006; Lau et al., 2007; Treiber et al., 2007; Gui et al., 2008; Annaert et al., 2010; Bednarczyk, 2010; Gui et al., 2010; Leonhardt et al., 2010
Rifamycin SV	0.171–2	Vavricka et al., 2002; Campbell et al., 2004; Chen et al., 2005; Hirano et al., 2006; Seithel et al., 2007; Sharma et al., 2009
Ritonavir	0.71–1.4	Tirona et al., 2003; Hirano et al., 2006; Annaert et al., 2010
Rosiglitazone	6.0	Nozawa et al., 2004; Bachmakov et al., 2008
Roxithromycin	153	Seithel et al., 2007
Saquinavir	1.2–1.8	Tirona et al., 2003; Campbell et al., 2004; Hirano et al., 2006; Annaert et al., 2010
Sildenafil	1.5	Treiber et al., 2007
Simvastatin	+	Hsiang et al., 1999
Simvastatin acid	3.6	Nakai et al., 2001; Chen et al., 2005
Simvastatin lactone	9.7	Chen et al., 2005
Sirolimus	6.49	Oswald et al., 2010
SN-38	+	Nozawa et al., 2005
Tacrolimus	0.611–3.7	Fehrenbach et al., 2003; Hirano et al., 2006; Amundsen et al., 2010
Telithromycin	121	Seithel et al., 2007
Telmisartan	0.436	Hirano et al., 2006

TABLE 5
Continued

Inhibitor	IC_{50} or K_i	Reference
	μM	
Thyroxine	3.5–3.85	Gui et al., 2009; Bednarczyk, 2010
Troglitazone	1.0–1.2	Gui et al., 2008, 2009
Troglitazone sulfate	+	Nozawa et al., 2004
Valsartan	8.96	Hirano et al., 2006
Valspodar	+	Oostendorp et al., 2009
Verapamil	+	Oostendorp et al., 2009
Zosuquidar	+	Oostendorp et al., 2009; Leonhardt et al., 2010

Gd-EOB-DTPA, gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid; IC_{50}, inhibitor concentration producing 50% inhibition of transporter activity; SN-38, an active metabolite of irinotecan; +, inhibits OATP1B1, but IC_{50}/K_i not available.

tions and the risk of myopathy, without an equivalent increase in cholesterol-lowering efficacy.

In a genome-wide association study on methotrexate pharmacokinetics in children with acute lymphoblastic leukemia, the *SLCO1B1* variants associated with an enhanced clearance of methotrexate were associated with an increased risk of gastrointestinal toxicity during consolidation therapy (odds ratio, 16.4 for rs11045879 and 15.3 for rs4149081 variant allele) (Treviño et al., 2009). This can be explained by the enhanced hepatic uptake and biliary clearance of methotrexate increasing the intestinal exposure to the intravenously administered methotrexate. The *SLCO1B1* c.521T>C SNP showed a borderline significant protective effect from gastrointestinal toxicity (Treviño et al., 2009). It is tempting to speculate that *SLCO1B1* genotyping could be used to identify those children with acute lymphoblastic leukemia who are susceptible to gastrointestinal toxicity of methotrexate and to tailor their treatment and follow-up accordingly.

B. Inhibition of Organic Anion Transporting Polypeptide 1B1

1. Inhibitors. Several clinically used drugs have been found to inhibit OATP1B1 transport activity in vitro (Table 5). Many of the inhibitors are not OATP1B1 substrates, even though substrates can competitively inhibit other substrates that interact at the same site of OATP1B1. The most potent OATP1B1 inhibitors, showing inhibition constant (K_i) or 50% inhibitory concentration (IC_{50}) values below 1 μM for at least some substrates, include atorvastatin, the dopamine agonist bromocriptine, bromosulfophthalein, the immunosuppressant cyclosporine, the estrone-3-sulfate derivative estropipate, glyburide, indocyanine green, lopinavir, nelfinavir, paclitaxel, rifampin, rifamycin SV, ritonavir, tacrolimus, and telmisartan (Nakai et al., 2001; Vavricka et al., 2002; Fehrenbach et al., 2003; Shitara et al., 2003; Tirona et al., 2003; Campbell et al., 2004; Chen et al., 2005; Fischer et al., 2005; Hirano et al., 2006; Ho et al., 2006; Seithel et al., 2007; Treiber et al., 2007; Gui et al., 2008, 2009; Sharma et al., 2009; Amundsen et al., 2010; Annaert et al., 2010; Bednarczyk, 2010; Gui et al., 2010; Han et al., 2010). The large differences in the K_i or IC_{50} values of individual inhibitors on different substrates supports the idea that OATP1B1 may have multiple substrate binding sites.

It should be recognized that many OATP1B1 inhibitors are also potent inhibitors of other transporters (especially OATP1B3) or drug-metabolizing enzymes. For example, cyclosporine is an inhibitor of the P-glycoprotein, OATP1B3, OATP2B1, BCRP, MRP2, and CYP3A4 (Rao and Scarborough, 1994; Shitara et al., 2003; Ho et al., 2006) (Stapf et al., 1994; Chen et al., 1999; Kajosaari et al., 2005b; Xia et al., 2007). In a recent study, estropipate was found to have a relatively high selectivity for OATP1B1 inhibition (IC_{50} = 0.06 μM) compared with OATP1B3 inhibition (IC_{50} = 19.3 μM) (Gui et al., 2010). It is not known whether estropipate inhibits OATP2B1.

If a drug shows an IC_{50} or K_i value less than 10 times the unbound peak plasma concentration, then the compound may be an inhibitor of OATP1B1 in vivo (Giacomini et al., 2010). The anticipated degree of interaction in vivo can be extrapolated by calculating the R value, as is usually done for in vitro-in vivo extrapolation of metabolic drug-drug interactions (Ito et al., 1998). The R value is defined as $1 + (f_u \times I_{in,max}/IC_{50})$, in which $I_{in,max}$ is the estimated maximum inhibitor concentration at the inlet to the liver and is equal to $I_{max} + (f_a \times \text{Dose} \times k_a/Q_h)$. I_{max} is the maximum systemic plasma concentration of the inhibitor, f_u is the fraction of inhibitor unbound in plasma, f_a is the fraction of the dose of the inhibitor that is absorbed, k_a is the absorption rate constant of the inhibitor, and Q_h is the hepatic blood flow. If a substrate drug is eliminated completely via the liver and the fraction of hepatic uptake mediated by OATP1B1 is 100%, then the R value corresponds to substrate drug $AUC_{inhibited}/AUC_{control}$. Because of a lack of validated specific substrates and inhibitors useful for in vivo studies in humans, the predictivity of in vitro OATP1B1 inhibition data for humans in vivo is not yet well established. In a recent study, predictions based on in vitro inhibition data for 19 P-glycoprotein inhibitors showed a poor correlation with the degree of drug-drug interaction observed with the P-glycoprotein probe substrate digoxin in vivo in humans (Fenner et al., 2009).

2. Role in Drug-Drug Interactions. Many OATP1B1 substrates are also substrates of other drug transporters and are often subject to metabolism by cytochrome P450

enzymes, which makes estimation of the role of a single transporter from in vitro data challenging (Niemi, 2007; Kalliokoski and Niemi, 2009; Giacomini et al., 2010). Despite these limitations, several drug-drug interactions observed in vivo in humans can be at least partly attributed to inhibition of OATP1B1 (Table 6).

Cyclosporine markedly raises the plasma concentrations of several OATP1B1 substrate drugs, such as statins (Table 6, Fig. 7). Cyclosporine has raised the AUC of atorvastatin approximately 7- to 15-fold, that of cerivastatin 4-fold, that of fluvastatin 3- to 4-fold, that of lovastatin 20-fold, that of pravastatin 5- to 10-fold, that of pitavastatin 5-fold, that of rosuvastatin 7-fold, and that of simvastatin approximately 3- to 8-fold (Arnadottir et al., 1993; Regazzi et al., 1993; Olbricht et al., 1997; Mück et al., 1999; Åsberg et al., 2001; Ichimaru et al., 2001; Park et al., 2001; Hasunuma et al., 2003; Hedman et al., 2004; Hermann et al., 2004; Simonson et al., 2004; Lemahieu et al., 2005). Although inhibition of CYP3A4 may partly explain the effects of cyclosporine on simvastatin, lovastatin, atorvastatin, and cerivastatin, the other statins, rosuvastatin, pravastatin, and pitavastatin, are not significantly metabolized by CYP3A4 (Neuvonen et al., 2006). In contrast to the effects of cyclosporine, tacrolimus has not affected the plasma concentrations of atorvastatin or simvastatin (Ichimaru et al., 2001; Lemahieu et al., 2005), suggesting that tacrolimus does not inhibit OATP1B1 in vivo in humans.

In one study, cyclosporine (two 100-mg doses 13 and 1 h before repaglinide) raised the AUC of repaglinide approximately 2.4-fold (Kajosaari et al., 2005b). It is noteworthy that the increase was 42% smaller in subjects with the *SLCO1B1* c.521TC genotype than in those with the reference c.521TT genotype, supporting the role of OATP1B1 in the interaction (Kajosaari et al., 2005b). Cyclosporine has also increased the AUC of bosentan approximately 2-fold, that of caspofungin 1.4-fold, that of the SN-38 active metabolite of irinotecan 1.2- to 7.3-fold, and that of methotrexate 1.3-fold Binet et al., 2000; Fox et al., 2003; Innocenti et al., 2004; Merck and Co., 2010). Although inhibition of CYP3A4 and transporters other than OATP1B1 may explain some interactions of cyclosporine, it seems reasonable to assume that inhibition of OATP1B1-mediated hepatic uptake at least contributes to the clinically observed drug-drug interactions caused by cyclosporine.

TABLE 6
Examples of drug-drug interactions caused by inhibition of OATP1B1

Inhibitor	Substrate	AUC Increase	Reference
		fold	
Atazanavir/ritonavir	Rosuvastatin	2.1	Busti et al., 2008
Atorvastatin	Repaglinide	1.2	Kalliokoski et al., 2008a
Clarithromycin	Pravastatin	2.1	Jacobson, 2004
Cyclosporine	Bosentan	2	Binet et al., 2000
	Caspofungin	1.4	Merck and Co., 2010
	Atorvastatin	7.4[a]	Åsberg et al., 2001
		8.7[a]	Hermann et al., 2004
		15.3[a]	Lemahieu et al., 2005
	Cerivastatin	3.8[a]	Mück et al., 1999
	Fluvastatin	3.1–3.6	Park et al., 2001
	Irinotecan	1.2–7.3 (SN-38)	Innocenti et al., 2004
	Lovastatin	20[a]	Olbricht et al., 1997
	Methotrexate	1.2	Fox et al., 2003
	Pitavastatin	5	Hasunuma et al., 2003
	Pravastatin	10	Regazzi et al., 1993
		5–7	Olbricht et al., 1997
		9.9	Hedman et al., 2004
	Repaglinide	2.4[a]	Kajosaari et al., 2005b
	Rosuvastatin	7.1	Simonson et al., 2004
	Simvastatin	2.6[a]	Arnadottir et al., 1993
		8[a]	Ichimaru et al., 2001
Eltrombopag	Rosuvastatin	1.6	European Medicines Agency, 2010a
Gemfibrozil	Atorvastatin	1.2	Backman et al., 2005
	Cerivastatin	5.6[b]	Backman et al., 2002
	Fluvastatin	No change	Spence et al., 1995
	Lovastatin	2.8	Kyrklund et al., 2001
	Pitavastatin	1.5	Mathew et al., 2004
	Pravastatin	2	Kyrklund et al., 2003
	Repaglinide	8.1[b]	Niemi et al., 2003c
	Rosuvastatin	1.9	Schneck et al., 2004
	Simvastatin	2.9	Backman et al., 2000
Lopinavir/ritonavir	Rosuvastatin	2.1	Kiser et al., 2008
Rifampin[c]	Atorvastatin	7.3	Lau et al., 2007
	Atorvastatin	4.3–9.3	He et al., 2009
	Glyburide	2.3	Zheng et al., 2009

[a] Inhibition of CYP3A4 also involved.
[b] Inhibition of CYP2C8 is probably the main mechanism of the interaction.
[c] Single-dose administration.

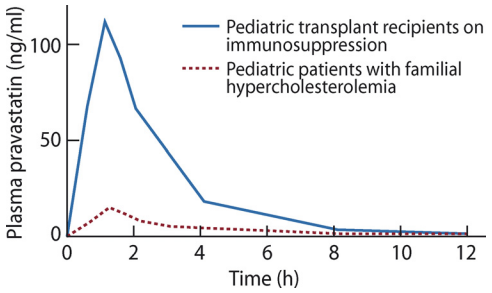

FIG. 7. Mean plasma concentrations of pravastatin after a single 10-mg oral dose of pravastatin in children with familial hypercholesterolemia and in transplant recipient children on an immunosuppressive therapy containing cyclosporine. [Reproduced from Hedman M, Neuvonen PJ, Neuvonen M, Holmberg C, and Antikainen M (2004) Pharmacokinetics and pharmacodynamics of pravastatin in pediatric and adolescent cardiac transplant recipients on a regimen of triple immunosuppression. *Clin Pharmacol Ther* **75**:101–109. Copyright © 2004 Nature Publishing Group. Used with permission.]

Also gemfibrozil has markedly raised the plasma concentrations of several OATP1B1 substrate drugs, such as atorvastatin and its active metabolites (1.2- to 1.8-fold increased AUC), cerivastatin (5.6-fold), lovastatin (2.8-fold), pravastatin (2.2-fold), rosuvastatin (1.9-fold), repaglinide (8.1-fold), and simvastatin acid (2.9-fold) (Backman et al., 2000, 2002, 2005; Kyrklund et al., 2001, 2003; Niemi et al., 2003b; Schneck et al., 2004). Gemfibrozil and, in particular, its glucuronide conjugate are potent inhibitors of CYP2C8 (Shitara et al., 2004; Ogilvie et al., 2006), which probably mainly explains the effects of gemfibrozil on cerivastatin and repaglinide. Moreover, the finding that the *SLCO1B1* genotype had no effect on the relative increase in repaglinide AUC by gemfibrozil suggests that inhibition of OATP1B1 is of minor importance in the interaction between gemfibrozil and repaglinide (Kalliokoski et al., 2008a). However, as pravastatin and rosuvastatin are not metabolized via CYP2C8 and simvastatin is metabolized via CYP2C8 to a minor extent only, the interactions of gemfibrozil with these drugs may be mainly explained by inhibition of OATP1B1 by gemfibrozil and its glucuronide (Schneck et al., 2004; Shitara et al., 2004; Hirano et al., 2006; Ho et al., 2006; Noé et al., 2007).

The antituberculosis drug rifampin, which is known for its strong inducing effect on drug-metabolizing enzymes (Niemi et al., 2003a), is a relatively potent inhibitor of OATP1B1 and OATP1B3 in vitro (Vavricka et al., 2002; Tirona et al., 2003; Hirano et al., 2006; Lau et al., 2007; Treiber et al., 2007; Gui et al., 2008; Annaert et al., 2010; Bednarczyk, 2010; Gui et al., 2010; Leonhardt et al., 2010). In one study, a single 600-mg intravenous dose of rifampin raised the mean AUC of atorvastatin by more than 600%, probably by inhibiting OATP1B1- and/or OATP1B3-mediated hepatic uptake of atorvastatin (Lau et al., 2007). In another recent study (He et al., 2009), a single oral dose of 600 mg of rifampin increased the AUC of atorvastatin approximately 9-, 6-, and 4-fold among individuals with the *SLCO1B1* c.521TT, c.521TC, and c.521CC genotype, respectively; i.e., the interaction was dependent on the *SLCO1B1* genotype. In addition to OATP1B1 and OATP1B3, rifampin inhibits also other transporters, such as P-glycoprotein (Fardel et al., 1995), and various cytochrome P450 enzymes, such as CYP3A4 and CYP2C8. However, the K_i value of rifampin for inhibition of OATP1B1 (0.477–17 μM) (Vavricka et al., 2002; Tirona et al., 2003; Hirano et al., 2006; Lau et al., 2007; Treiber et al., 2007; Gui et al., 2008; Annaert et al., 2010; Bednarczyk, 2010; Gui et al., 2010; Leonhardt et al., 2010) is lower than that for CYP3A4 (18.5 μM) or CYP2C8 (30.2 μM) (Kajosaari et al., 2005a). However, repeated dosing of rifampin, which has a short half-life of approximately 2 to 3 h and is usually given once daily, within a few days causes a strong induction of, for example, CYP3A4 and CYP2C8 (Niemi et al., 2003a). Rifampin also induces P-glycoprotein and MRP2 via a PXR-dependent mechanism in human intestine (Greiner et al., 1999; Fromm et al., 2000) and OATP1B1 in primary human hepatocytes (Jigorel et al., 2006; Sahi et al., 2006). Thus, in clinical use, rifampin decreases the plasma concentrations of most statins and other OATP1B1 substrates (Kyrklund et al., 2000, 2004; Backman et al., 2005). Nevertheless, rifampin can be used as a model inhibitor of OATP1B1 in vitro and in single dose studies also in humans.

Concomitant use of ritonavir (100 mg)-boosted lopinavir (400 mg) has raised the AUC and peak plasma concentration (C_{max}) of rosuvastatin by ~2- and 4.7-fold, respectively (Kiser et al., 2008). Likewise, ritonavir (100 mg)-boosted atazanavir (300 mg) has raised the AUC and C_{max} of rosuvastatin by approximately 2.1- and 7-fold, respectively (Busti et al., 2008). Both lopinavir and atazanavir are more potent inhibitors of OATP1B1 than of OATP1B3 and do not inhibit OATP2B1 (Annaert et al., 2010). Their interactions with rosuvastatin are thus probably caused mainly by inhibition of OATP1B1, with contribution from inhibition of OATP1B3. On the other hand, nelfinavir, 1250 mg twice daily, has decreased the AUC and C_{max} of pravastatin by approximately 47 and 40%, respectively, by an unknown mechanism (Aberg et al., 2006).

The macrolide antibiotics clarithromycin, erythromycin, and telithromycin are known mechanism-based inhibitors of CYP3A4, and thus markedly raise, for example, the plasma concentrations of CYP3A4-metabolized statins (Kantola et al., 1998; Neuvonen et al., 2006). However, clarithromycin (500 mg twice daily) has also raised the AUC of pravastatin 2.1-fold, probably by inhibiting OATP1B3 and OATP1B1 (Jacobson, 2004). On the other hand, erythromycin, 500 mg four times daily, did not increase rosuvastatin exposure (Cooper et al., 2003).

Inhibitors of OATP1B1, such as cyclosporine, gemfibrozil, lopinavir/ritonavir, and atazanavir/ritonavir, can substantially diminish the therapeutic index of most statins (Neuvonen et al., 2006; Neuvonen, 2010). Hepatocyte is a target site for the pharmacological action of all statins, whereas their myotoxic effects are associated

with the peripheral plasma concentrations of statins, their metabolites, and lactones. OATP1B1 inhibitors increase the ratio between plasma and hepatocyte statin concentrations [i.e., decrease the benefit (cholesterol-lowering effect) to risk (skeletal muscle toxicity) ratio of OATP1B1-dependent statins]. The clinical significance of statin interactions mediated by the inhibition of the hepatic uptake seems to be greater than of those mediated by the inhibition of cytochrome P450 enzymes only. Concomitant inhibition of both OATP1B1 and metabolizing enzymes (e.g., of CYP3A4 or CYP2C8) by drugs such as cyclosporine, ritonavir, or gemfibrozil can further increase the clinical significance of the statin interactions.

In addition to being susceptible to OATP1B1 inhibition, atorvastatin is also a weak inhibitor of OATP1B1 in vivo. In healthy subjects, atorvastatin has slightly increased the AUC of repaglinide in persons with the *SLCO1B1*1A/*1A* genotype (by ~20%) and the C_{max} of repaglinide in those with the *SLCO1B1*1A/*1A* (~40%) or *SLCO1B1* c.521TC (by ~30%) genotype, without inhibiting the CYP3A4- and CYP2C8-mediated metabolism of repaglinide (Kalliokoski et al., 2008a).

3. Points to Consider When Investigating OATP1B1-Mediated Drug Interactions. The use of easily detectable probe substrates (e.g., fluorescent or radiolabeled compounds) allows the screening of multiple compounds for potential inhibitory effect on OATP1B1 with a relatively high throughput (Bednarczyk, 2010). However, there seem to be multiple substrate and inhibitor binding sites in OATP1B1. To more accurately reflect the potential for inhibition of OATP1B1 in vivo, such high-throughput methods should therefore be validated against a clinically important OATP1B1 substrate. The predictivity of high-throughput methods might also be improved by using multiple OATP1B1 substrates with distinct transport kinetics, increasing the likelihood that multiple binding sites are covered. If a potential OATP1B1 inhibitor is identified using a screening approach, it is recommended to follow-up the screening studies by characterizing the inhibitory potency of the compound in detail on multiple OATP1B1 substrates, including clinically important drug substrates.

Several points need to be considered when selecting a probe substrate for investigating the inhibitory effect of a compound on OATP1B1 in vivo in humans. First, it is important to select a probe substrate that has been shown to be susceptible to differences in OATP1B1 activity (e.g., sensitivity to *SLCO1B1* polymorphism and OATP1B1 inhibitors). In addition, it is recommended that the selection of an in vivo probe substrate is supported by in vitro data on the effects of the suspected inhibitor on the transport of the probe substrate, to rule out the possibility of substrate-specific lack of inhibition. Of note is that cell-based assays may be challenging for some clinically important OATP1B1 substrates due to their physicochemical properties, such as relatively high lipophilicity (e.g., simvastatin acid). Furthermore, the probe substrate should preferably be a clinically important substrate, so that the results of a drug interaction study can be directly employed to enhance drug safety. Moreover, the contribution of other influx transporters (e.g., OATP1B3 and OATP2B1) to the hepatic uptake of the probe substrate should be considered as well as the potential of the inhibitor to inhibit these. Likewise, the contribution of drug metabolism to the clearance of the probe substrate and the potential of the inhibitor to inhibit these processes should also be considered.

Potential in vivo probe substrates for OATP1B1 include simvastatin (acid), pitavastatin, atorvastatin, pravastatin, and rosuvastatin (Niemi, 2010). All of these have their pros and cons. Simvastatin and atorvastatin are highly sensitive to altered OATP1B1 activity and clearly clinically important substrates. However, they are metabolized to a significant extent by CYP3A4, and the potential of the inhibitor to inhibit CYP3A4 should also be considered both in vitro and in vivo. Pitavastatin seems to be almost as sensitive a substrate of OATP1B1 as simvastatin, but its use may be limited by availability, because it is not yet available for clinical use, for example, in Europe. Although pravastatin and rosuvastatin are not significantly metabolized and are widely available, they are somewhat less susceptible to differences in OATP1B1 activity than, for example, simvastatin, and particular attention should be paid to the contribution of other OATP transporters to their interactions. Plasma concentrations of endogenous OATP1B1 substrates (e.g., bilirubin) may also be considered as additional markers for OATP1B1 activity, but further studies are required on their susceptibility to OATP1B1 inhibition and on the time course of changes in their concentrations as a result of OATP1B1 inhibition.

The most specific way to investigate the contribution of OATP1B1 to the hepatic uptake of a compound in vivo is to carry out a pharmacokinetic study in persons with *SLCO1B1* SNPs associated with impaired OATP1B1 activity. In addition, cyclosporine, gemfibrozil, and rifampin have been employed as probe inhibitors for OATP1B1 in vivo. However, it is important to recognize that none of these drugs is a specific inhibitor of OATP1B1; e.g., cyclosporine is a potent inhibitor of OATP1B3, OATP2B1, P-glycoprotein, and CYP3A4 (Stapf et al., 1994; Kajosaari et al., 2005b; Ho et al., 2006), gemfibrozil is a potent inhibitor of CYP2C8 (Backman et al., 2002; Ogilvie et al., 2006), and rifampin is a potent inhibitor of OATP1B3, CYP2C8, and CYP3A4 (Vavricka et al., 2002; Kajosaari et al., 2005a). Moreover, the inhibitory effects of rifampin are short lasting, whereas its potent inducing effects on drug-metabolizing enzymes and transporters dominate during multiple dosing (Niemi et al., 2003).

V. Conclusion and Future Prospects

Studies on the pharmacogenetics of *SLCO1B1* and on OATP1B1-mediated drug-drug interactions have demonstrated that OATP1B1 is crucial for the efficient hepatic

uptake of many drugs with variable chemical structures and clinical uses. Impaired OATP1B1 activity results in decreased hepatic uptake, increased plasma concentrations, and altered response to many drugs. OATP1B1 is one of the most important drug transporters in humans and the pharmaceutical industry is endorsed to investigate possible interactions of new drug candidates with OATP1B1 (Giacomini et al., 2010), especially those that possess physicochemical and disposition characteristics similar to known OATP1B1 substrates and inhibitors (Tables 1, 2, and 5). During drug development, OATP1B1 studies should be undertaken to clarify the possible role of OATP1B1 in a drug candidate's disposition, efficacy, and safety.

The evidence gathered so far indicate a broad substrate and inhibitor specificity for OATP1B1, and its substrate and inhibitor lists are likely to grow substantially in the next years. Although several well established methods exist for studying interactions of compounds with OATP1B1 in vitro, the quantitative in vitro-in vivo prediction for OATP1B1 is still poorly validated. In vivo studies on OATP1B1 in humans are limited by the lack of suitable specific probe substrates and inhibitors. Methods such as physiologically based pharmacokinetic modeling and cell lines transfected with multiple transporters and/or drug-metabolizing enzymes may help in estimating the relative contributions of OATP1B1 and other closely related OATPs, other drug transporters, and drug metabolizing enzymes to the absorption and disposition of a drug. A specific and relevant way to investigate the contribution of OATP1B1 to the hepatic uptake of a compound in vivo, is to investigate its disposition in persons with *SLCO1B1* SNPs associated with decreased OATP1B1 activity. Moreover, pharmacogenetic association studies are useful for investigating the role of OATP1B1 in various drug response traits (e.g., organ toxicity).

Genotyping for selected *SLCO1B1* variants (c.521T>C) can already now be recommended to improve the safety and efficacy of, for example, statin therapy (Niemi, 2010), and in the future probably of other drug therapies as well. However, further studies are required to more fully characterize genetic variability in the *SLCO1B1* locus and to work out the molecular mechanisms involved in some associations of *SLCO1B1* variants with OATP1B1 function. Furthermore, method development should help to differentiate the contributions of OATP1B1, OATP1B3, and OATP2B1 to the hepatic uptake of compounds. The availability of advanced next generation sequencing methods may facilitate this area of research. Finally, knowledge about OATP1B1-mediated drug-drug interactions will help the clinician to avoid potentially harmful drug combinations in the treatment of patients with various diseases.

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Wrote or contributed to the writing of the manuscript: Niemi, Pasanen, and Neuvonen.

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