reviews

molecular pharmaceutics

Hepatic OATP1B Transporters and Nuclear Receptors PXR and CAR: Interplay, Regulation of Drug Disposition Genes, and Single Nucleotide Polymorphisms

Henriette E. Meyer zu Schwabedissen[†,‡] **and Richard B. Kim***[,‡]

Department of Pharmacology, Ernst Moritz Arndt University of Greifswald, Greifswald, Germany, and Division of Clinical Pharmacology, Department of Medicine, University of Western Ontario, London, Ontario, Canada

Received January 26, 2009; Revised Manuscript Received May 29, 2009; Accepted June 26, 2009

Abstract: Drug uptake transporters are now increasingly recognized as clinically relevant determinants of variable drug responsiveness and unexpected drug−drug interactions. Emerging evidence strongly suggests members of the organic anion transporting polypeptide (OATP) family appear to be particularly important to the disposition of many drugs in clinical use today. Specifically, the liver-enriched OATP1B subfamily members OATP1B1 and OATP1B3 exhibit broad substrate specificity and the ability to transport drugs which are ligands for xenobiotic sensing nuclear receptors such as the pregnane X receptor (PXR) and the constitutive androstane receptor (CAR). Accordingly, OATP1B transporters may indirectly regulate expression of drug metabolism genes *via* modulation of the intracellular concentration of PXR and CAR ligands. Moreover, a number of functionally important single nucleotide polymorphisms (SNPs) in OATP1B transporters have been described. In this review, a brief summary of known SNPs in PXR and CAR will be followed by an in-depth outline of OATP1B1 and OATP1B3 transporters particularly in relation to the known SNPs in these OATPs and the interplay between OATP1B transporters with PXR and CAR, both *in vitro* and *in vivo*.

Keywords: Organic anion transporting polypeptide; single nucleotide polymorphism; nuclear receptor; transactivation; pregnane X receptor; constitutive androstane receptor; vitamin D receptor; farnesoid X receptor

Introduction

Extent of intersubject variation in drug metabolism has long been considered to be a critical factor governing variable drug efficacy and toxicity. It is currently thought that genetic variation typically accounts for 15%−30% of interindividual differences in drug metabolism and response, although for some drugs that can be as high as 95%.[1] Interestingly, for a number of key CYP enzymes such as members of the CYP3A subfamily, which are generally thought to be involved in the metabolic biotransformation of nearly 50% of all the drugs in clinical use,[2] variability in expression does not appear to be related to single nucleotide polymorphisms (SNPs), despite the known marked interindividual variability observed in CYP3A function,[3] both *in vitro* and *in vivo*. Indeed when drug interactions that reduce CYP3A activity or enhance the expression through induction are considered, the net observed variation in CYP3A activity is thought to span nearly 400-fold.[4,5]

* Corresponding author: Richard B. Kim, M.D.; ALL-152 LHSC−University Hospital, 339 Windermere Road, London, Ontario, N6A 5A5, Canada. Tel: 519 663 3553. Fax: 519 663 3232. E-mail: richard.kim@lhsc.on.

† Ernst Moritz Arndt University of Greifswald.

‡ University of Western Ontario.

(1) Eichelbaum, M.; Ingelman-Sundberg, M.; Evans, W. E. Pharmacogenomics and Individualized Drug Therapy. *Annu. Rev. Med.* **2006**, *57*, 119–137.

(2) Bertz, R. J.; Granneman, G. R. Use of in Vitro and in Vivo Data to Estimate the Likelihood of Metabolic Pharmacokinetic Interactions. *Clin. Pharmacokinet.* **1997**, *32*, 210–258.

(3) Ozdemir, V.; Kalow, W.; Tang, B. K.; Paterson, A. D.; Walker, S. E.; Endrenyi, L.; Kashuba, A. D. Evaluation of the Genetic Component of Variability in CYP3A4 Activity: a Repeated Drug Administration Method. *Pharmacogenetics* **2000**, *10*, 373–388.

10.1021/mp9000298 CCC: $40.75
Published on Web 06/26/2009

Table 1. List of Known PXR Agonists and Antagonists[a]

PXR Inducers			
aldrin	cypermethrin	isradipine	rifaximin
artemisinin	DDT	LK-935	ritonavir
atorvastatin	dexamethasone	lovastatin	RU-58668
BK 8644	dex-*t*-butylacetate,	lindane	simvastatin
bisphenol A	dicloxacillin	meconazole	spironolactone
bupirimate	dieldrin	mevastatin	SR 12813
carbamazepin	docetaxel	methoxychlor	sulfisoxazole
aldrin	econazole	metolachlor	sulfinpyrazone
cerivastatin	efavirenz	mifepristone (RU486)	tamoxifen
chlordecone	endosulfan	nafcillin	tanshinone IIA[b]
chlordane	erlotinib	nicardipine	paclitaxel
chlorpyrifos	fluvastatin	nifedipine	tetracyclin
cisplatin	fenvalerate	oxadiazon	TO-901317
clindamycin	ginko biloba extract	oxiconazole	topiramate
clotrimazole	griseofluvin	paclitaxel	*trans*-nonachlor
colupulone[c]	4-hydroxtamoxifen	pretilachlor	troleandomycin
crypterone acetate	hyperforin[d]	pentachlorophenol	valproate
cryptotanshinone[b]	ifosfamide	reserpin	α-zearalenol
cyclophosphamide	ICI 182780	rifampin (human specific)	α-zearalanone
[1-(2-chlorophenyl)-*N*-[1-(1-phenylethyl)-1*H*-benzimidazol-5-yl]methanesulfonamide]			
1-(2-chlorophenylmethylpropyl)-3-isoquinoline-carboxamide (PK11195)			

Endogenous PXR Agonists		
androst-5-ene-3β,17β-diol,	6,16-dimethylpregnenolone	5β-pregane-3,20-dione
androst-5-ene-3,17-dione	17β-estradiol	progesterone
24(*S*),25-epoxycholesterol	estrone	17-OH-progesterone
5β-cholestan-3α,7α,12α-triol	7α-hydroxycholesterol	taurine conjugated bile acids
corticosterone	17-hydroxypregnenolone	ursodeoxycholicacid (UDCA)
dihydroepiandrosterone (DHEA)	lithocholic acid (LCA)	
dihydrotestosterone	pregnenolone	

PXR Antagonists		
A-76911	fluconazole	ketoconazole
enilconazole	trabectedin (ET-743)	

[a] References provided upon request. [b] Constituent of danshen. [c] Constituent of hops. [d] Constituent of St. John's wort.

There is now an emerging acceptance of the critical role of drug uptake transporters; particularly those expressed in organs such as the liver not only play a direct role in the hepatic elimination of substrate drugs but are of relevance to drug metabolism through alteration of the hepatic concentration of endo- and xenobiotic compounds that interact with nuclear receptors such as PXR and CAR, and thereby directly alter the extent of target gene transcription, including major CYP enzymes such as CYP3A4. Specifically, members of the OATP1B subfamily of sodium-independent uptake transporter expressed in liver are increasingly recognized for their ability to transport a large array of structurally divergent compounds including xenobiotics and hormones that function as ligands for nuclear receptors PXR (Table 1) and CAR (Table 2). In this review, a brief overview of nuclear receptors PXR and CAR will be followed by a more in-depth review of hepatic OATP1B transporters. In addition, the extent of known single nucleotide polymorphisms (SNPs) in PXR, CAR and OATP1B transporters will be outlined as such SNPs may exhibit clinical relevance *via* alteration in the expression of drug metabolizing enzymes.

The Interplay of Drug Transporters, Nuclear Receptors and Drug Metabolizing Enzyme: The Conceptual Framework

Drug concentration is determined by the extent of drug absorption, distribution, metabolism and elimination (ADME). For many drugs, the liver is the main organ for metabolism and elimination. And for several drugs, the observed avid hepatic extraction is dependent on carrier-mediated processes, broadly referred to as hepatic uptake transporters. Once a drug gains access into the hepatocyte, the process of

(4) Thummel, K. E.; Wilkinson, G. R. In Vitro and in Vivo Drug Interactions Involving Human CYP3A. *Annu. Rev. Pharmacol. Toxicol.* **1998**, *38*, 389–430.

(5) Wilkinson, G. R. Drug Metabolism and Variability Among Patients in Drug Response. *N. Engl. J. Med.* **2005**, *352*, 2211–2221.

Table 2. List of Known CAR Agonists and Antagonists[a]

CAR Agonists		
artesiminin	CITCO	phenytoin
atorvastatin	efavirenz	phenobarbital
carbamazepin	fluvastatin	simvastatin
cerivastatin	nevirapine	tri-*p*-methylphenyl phosphate (TMPP)
CAR Agonists (Mouse Specific)		
chlorpromazine	meclizine	1,4-bis[2-(3,5-dichloropyridyloxy)]-benzene (TCPOBOP)
17α-ethynyl-3,17β-estradiol		
CAR Antagonists		
clotrimazole		PK-11195

[a] References provided upon request.

metabolism and elimination of both the parent compound and the metabolite *via* biliary efflux transporters ensures efficient removal of xenobiotics and limits systemic exposure to potential toxins. It is clear that the maintenance of regulated expression of both drug transporters and metabolizing enzymes is governed through the activation of intracellular "xenosensors". These ligand-activated transcription factors sense the intracellular level of xenobiotics and, upon ligand binding, translocate into the nucleus and transcriptionally activate genes involved in xenobiotic metabolism and transport. Therefore it is assumed that nuclear receptors play a pivotal role in drug disposition and hepatoprotection. Interestingly, members of the OATP1B subfamily can mediate the hepatocellular uptake of ligands for xenosensors such as PXR and CAR, and thereby function as a potential rate limiting step for their activation.

Nuclear Reports-Intracellular Xenobiotic Sensors

Nuclear receptors represent a family of transcription factors that function as modulators of gene expression. There are 49 members of this family which share three structural features including an amino terminal activation function 1 (AF-1) domain that is responsible for ligand independent activation, a DNA binding domain (DBD) that interacts with DNA response elements on target genes to modulate transcription, and, located at the carboxy terminus, a ligand-binding domain (LBD).[6,7] In general, the ligand free nuclear receptors reside in the cytoplasm, bound to corepressors that recruit specific histone deacetylase-containing complexes. Upon ligand binding, the activated nuclear receptor dissociates from the histone deacetylase-containing complex and translocates to the nucleus. In the nucleus, the ligand−receptor complex recruits coactivators forming homodimers or heterodimers and binds to the response elements in the regulatory (promoter and enhancer) regions of target genes leading to their transcriptional activation.[8] There are a number of excellent published reviews in relation to PXR and CAR. Similarly, an extensive literature exists regarding VDR, FXR, and LXR. In this review, we will focus mostly on single nucleotide polymorphism in PXR and CAR and how their substrate overlap with OATP1B transporters may affect the extent of their functional activation.

PXR (NR1I2) and Genetic Variation. PXR (NR1I2) is one of the members of the superfamiliy of nuclear receptors. PXR is a 434 amino acid, 50 kDa protein primarily expressed in liver and intestine,[9] the key organs that modulate drug disposition. In general PXR is assumed to function as an important mediator of drug−drug interactions due to its ability to be transactivated by an array of structurally divergent ligands (Table 1), while targeting genes that include enzymes and transporters of phase I to phase III biotransformation pathways (Table 5). The systematic assessment of compounds for their potential to interact with PXR appears to be particularly helpful in predicting induction related drug interactions involving CYP3A4 or MDR1. Ma et al. recently summarized the role of PXR knockout mice[10,11] in combination with humanized mouse models,[11−13] to assess the role of this nuclear receptor in drug−drug interactions observed *in vivo*.[14] Such studies clearly support an important func-

(6) Chawla, A.; Repa, J. J.; Evans, R. M.; Mangelsdorf, D. J. Nuclear Receptors and Lipid Physiology: Opening the X-Files. *Science* **2001**, *294*, 1866–1870.

(7) Bain, D. L.; Heneghan, A. F.; Connaghan-Jones, K. D.; Miura, M. T. Nuclear Receptor Structure: Implications for Function. *Annu. Rev. Physiol.* **2007**, *69*, 201–220.

(8) Urquhart, B. L.; Tirona, R. G.; Kim, R. B. Nuclear Receptors and the Regulation of Drug-Metabolizing Enzymes and Drug Transporters: Implications for Interindividual Variability in Response to Drugs. *J. Clin. Pharmacol.* **2007**, *47*, 566–578.

(9) Lehmann, J. M.; McKee, D. D.; Watson, M. A.; Willson, T. M.; Moore, J. T.; Kliewer, S. A. The Human Orphan Nuclear Receptor PXR Is Activated by Compounds That Regulate CYP3A4 Gene Expression and Cause Drug Interactions. *J. Clin. Invest.* **1998**, *102*, 1016–1023.

(10) Staudinger, J. L.; Goodwin, B.; Jones, S. A.; Hawkins-Brown, D.; MacKenzie, K. I.; LaTour, A.; Liu, Y.; Klaassen, C. D.; Brown, K. K.; Reinhard, J.; Willson, T. M.; Koller, B. H.; Kliewer, S. A. The Nuclear Receptor PXR Is a Lithocholic Acid Sensor That Protects Against Liver Toxicity. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 3369–3374.

(11) Xie, W.; Barwick, J. L.; Downes, M.; Blumberg, B.; Simon, C. M.; Nelson, M. C.; Neuschwander-Tetri, B. A.; Brunt, E. M.; Guzelian, P. S.; Evans, R. M. Humanized Xenobiotic Response in Mice Expressing Nuclear Receptor SXR. *Nature* **2000**, *406*, 435–439.

(12) Ma, X.; Cheung, C.; Krausz, K. W.; Shah, Y. M.; Wang, T.; Idle, J. R.; Gonzalez, F. J. A Double Transgenic Mouse Model Expressing Human Pregnane X Receptor and Cytochrome P450 3A4. *Drug Metab. Dispos.* **2008**, *36*, 2506–2512.

(13) Scheer, N.; Ross, J.; Rode, A.; Zevnik, B.; Niehaves, S.; Faust, N.; Wolf, C. R. A Novel Panel of Mouse Models to Evaluate the Role of Human Pregnane X Receptor and Constitutive Androstane Receptor in Drug Response. *J. Clin. Invest.* **2008**, *118*, 3228–3239.

(14) Ma, X.; Idle, J. R.; Gonzalez, F. J. The Pregnane X Receptor: From Bench to Bedside. *Expert. Opin. Drug Metab. Toxicol.* **2008**, *4*, 895–908.

Table 3. Single Nucleotide Polymorphisms Identified in the PXR (NR1I2) Gene Locus[a]

		position				allele frequency[c]				
dbSNP	location	NT 005612.15	*b*	nucleotide exchange	amino acid exchange	Db	Ca	AP	AA	JP
rs1063955	Exon 2	26021277	34	G>A	Ala12Thr	0.095				
rs59371185	Exon 2	26021295	52	G>A	Glu18Lys	nd[d]	0.000	0.014		
rs12721613	Exon 2	26021322	79	G>A	Pro27Ser	0.082	0.00/0.00	0.149	0.200	
	Exon 2	2621349	106	G>A	Gly36Arg		0.01−0.05	0.000	0.030−0.040	
	Exon 2	2621535	292	C>T	Arg98Cys				0.020	0.020
rs1140968	Exon 3	26024183	327	G>T	Lys109Asn	nd				
rs12721608	Exon 4	26025565	364	G>A	Arg122Gln	0.011	0.010−0.050			
	Exon 4	26025638	437	G>A	Val140Met		0.020	0.000		
	Exon 4	26025644	443	G>A	Arg148Gln					0.020
	Exon 4	26025720	474	C>G	Glu158Lys					
	Exon 4	26025689	488	A>G	Asp163Gly		0.000	0.014		
rs12721611	Exon 4	26025692	492	T>C	Thr164Thr	0.032				
rs35761343	Exon 8	26029772	1108	G>A	Ala370Thr	0.016	0.000	0.016		
	Exon 8	26029805	1141	C>T	Arg381Trp					0.020
	Exon 9	26029871	1207	G>A	Ile403Val					
rs56162473	Exon 9	26031176	1276	C>G	Gln426Glu	nd				

[a] References provided upon request. [b] From the translational initiation site or from the end of the nearest exon. [c] Db, database; Ca, Caucasians; AP, African population; AA, African Americans; JP, Japanese population. [d] Not determined.

tional role for PXR. Nevertheless translating findings from animal models is complicated by species differences in ligand binding specificity and differences in the promoter regions of regulated target genes.[15]

A number of studies have assessed the extent of genetic heterogeneity in the *NR1I2* gene among various human populations.[16−20] Single nucleotide polymorphisms in the coding region of the gene are summarized in Table 3. A number of identified nonsynonymous SNPs are located in presumably functionally important domains in PXR, such as the DNA binding domain (p.Gly36Arg, p.Arg98Cys and p.Arg122Gln) or the ligand binding domain (p.Arg148Gln, p.Glu158Lys, p.Asp163Gly, p.Ala370Thr, p.Arg381Trp and p.Ile493 Val). *In vitro* studies performed in a number of laboratories have revealed variable effects of PXR-variants in terms of target gene transactivation and have not yet resulted in reliable prediction of changes to induction *in vivo*. Nevertheless the nonsynonymous variants p.Arg98Cys, p.Arg148Gln, p.Glu158Lys, p.Arg381Trp and p.Ile403 Val have been shown to result in reduced PXR activity *in vitro* and therefore have the potential to contribute to interindividual variability in drug disposition.[21−23] Importantly, it should be noted that most of the identified SNPs in the coding region of *NR1I2* are rare and, thus, unlikely to be a major

(15) Tirona, R. G.; Leake, B. F.; Podust, L. M.; Kim, R. B. Identification of Amino Acids in Rat Pregnane X Receptor That Determine Species-Specific Activation. *Mol. Pharmacol.* **2004**, *65*, 36–44.

(16) Zhang, J.; Kuehl, P.; Green, E. D.; Touchman, J. W.; Watkins, P. B.; Daly, A.; Hall, S. D.; Maurel, P.; Relling, M.; Brimer, C.; Yasuda, K.; Wrighton, S. A.; Hancock, M.; Kim, R. B.; Strom, S.; Thummel, K.; Russell, C. G.; Hudson, J. R., Jr.; Schuetz, E. G.; Boguski, M. S. The Human Pregnane X Receptor: Genomic Structure and Identification and Functional Characterization of Natural Allelic Variants. *Pharmacogenetics* **2001**, *11*, 555–572.

(17) Hustert, E.; Zibat, A.; Presecan-Siedel, E.; Eiselt, R.; Mueller, R.; Fuss, C.; Brehm, I.; Brinkmann, U.; Eichelbaum, M.; Wojnowski, L.; Burk, O. Natural Protein Variants of Pregnane X Receptor With Altered Transactivation Activity Toward CYP3A4. *Drug Metab. Dispos.* **2001**, *29*, 1454–1459.

(18) King, C. R.; Xiao, M.; Yu, J.; Minton, M. R.; Addleman, N. J.; Van Booven, D. J.; Kwok, P. Y.; McLeod, H. L.; Marsh, S. Identification of NR1I2 Genetic Variation Using Resequencing. *Eur. J. Clin. Pharmacol.* **2007**, *63*, 547–554.

(19) Bosch, T. M.; Deenen, M.; Pruntel, R.; Smits, P. H.; Schellens, J. H.; Beijnen, J. H.; Meijerman, I. Screening for Polymorphisms in the PXR Gene in a Dutch Population. *Eur. J. Clin. Pharmacol.* **2006**, *62*, 395–399.

(20) Koyano, S.; Kurose, K.; Ozawa, S.; Saeki, M.; Nakajima, Y.; Hasegawa, R.; Komamura, K.; Ueno, K.; Kamakura, S.; Nakajima, T.; Saito, H.; Kimura, H.; Goto, Y.; Saitoh, O.; Katoh, M.; Ohnuma, T.; Kawai, M.; Sugai, K.; Ohtsuki, T.; Suzuki, C.; Minami, N.; Saito, Y.; Sawada, J. Eleven Novel Single Nucleotide Polymorphisms in the NR1I2 (PXR) Gene, Four of Which Induce Non-Synonymous Amino Acid Alterations. *Drug Metab. Pharmacokinet.* **2002**, *17*, 561–565.

(21) Koyano, S.; Kurose, K.; Saito, Y.; Ozawa, S.; Hasegawa, R.; Komamura, K.; Ueno, K.; Kamakura, S.; Kitakaze, M.; Nakajima, T.; Matsumoto, K.; Akasawa, A.; Saito, H.; Sawada, J. Functional Characterization of Four Naturally Occurring Variants of Human Pregnane X Receptor (PXR): One Variant Causes Dramatic Loss of Both DNA Binding Activity and the Transactivation of the CYP3A4 Promoter/Enhancer Region. *Drug Metab. Dispos.* **2004**, *32*, 149–154.

(22) Lim, Y. P.; Liu, C. H.; Shyu, L. J.; Huang, J. D. Functional Characterization of a Novel Polymorphism of Pregnane X Receptor, Q158K, in Chinese Subjects. *Pharmacogenet. Genomics* **2005**, *15*, 337–341.

(23) Owen, B. M.; Van Mil, S. W.; Boudjelal, M.; McLay, I.; Cairns, W.; Elias, E.; White, R.; Williamson, C.; Dixon, P. H. Sequencing and Functional Assessment of HPXR (NR1I2) Variants in Intrahepatic Cholestasis of Pregnancy. *Xenobiotica* **2008**, *38*, 1289–1297.

factor in PXR-mediated target gene activation in a given population. In contrast, SNPs in the untranslated regions of the gene are more frequent and have been linked to phenotypic changes such as altered target gene expression or doxorubicin clearance,[24,25] but published data to date have not been consistent.[26,27] It should be noted that genetic variants of PXR (namely, the -25385T>C and -24381A>C and -24113G>A linkage disequilibrium) have been associated with diseases including inflammatory bowel diseases (IBD) such as Crohn's disease and ulcerative colitis.[28,29] However, the overall contribution of PXR polymorphisms to complex multifactorial diseases such as ulcerative colitis or Crohn's disease needs additional prospective clinical studies.

Overall, there is little genetic variation in the PXR gene (nucleotide diversity of 1 in 15984bp of coding sequence in Caucasians),[16] which suggests evolutionary conservation of the gene and importance of this gene to the maintenance of drug disposition gene regulation.

Constitutive Androgen Receptor (CAR) and Genetic Variation. CAR, which is highly expressed in liver and intestine, shares a variety of target genes with PXR including CYP2B6,[30,31] CYP2C8,[32] CYP2C9,[33] CYP3A4,[34] CYP3A7,[35] MDR1,[36] MRP2,[37] and UGT1A1[38] (Table 5). In addition, CAR also heterodimerizes with its cognate partner RXR (retinoid X receptor).[39−41] However, in contrast to PXR, CAR exhibits high constitutive activity and is thought to play a significant role in maintaining the basal expression of target genes. Indeed, studies have shown that CYP2B6 and CYP3A4, which are normally absent in hepatoma cell lines, become detectable when CAR is introduced.[30,42] Transactivation mediated by CAR is thought to occur through multiple mechanisms. In addition to CAR ligands (Table 2), protein kinases,[43,44] protein phosphatases[45,46] and other factors[47] have been implicated in the modulation of CAR nuclear translocation. In addition, inverse agonism, where the binding of a ligand results in coactivator release and subsequent inhibitory effects, has been noted for

(24) Lamba, J.; Lamba, V.; Strom, S.; Venkataramanan, R.; Schuetz, E. Novel Single Nucleotide Polymorphisms in the Promoter and Intron 1 of Human Pregnane X Receptor/NR1I2 and Their Association With CYP3A4 Expression. *Drug Metab. Dispos.* **2008**, *36*, 169–181.

(25) Sandanaraj, E.; Lal, S.; Selvarajan, V.; Ooi, L. L.; Wong, Z. W.; Wong, N. S.; Ang, P. C.; Lee, E. J.; Chowbay, B. PXR Pharmacogenetics: Association of Haplotypes With Hepatic CYP3A4 and ABCB1 Messenger RNA Expression and Doxorubicin Clearance in Asian Breast Cancer Patients. *Clin. Cancer Res.* **2008**, *14*, 7116–7126.

(26) Hor, S. Y.; Lee, S. C.; Wong, C. I.; Lim, Y. W.; Lim, R. C.; Wang, L. Z.; Fan, L.; Guo, J. Y.; Lee, H. S.; Goh, B. C.; Tan, T. PXR, CAR and HNF4alpha Genotypes and Their Association With Pharmacokinetics and Pharmacodynamics of Docetaxel and Doxorubicin in Asian Patients. *Pharmacogenomics J.* **2008**, *8*, 139–146.

(27) Tham, L. S.; Holford, N. H.; Hor, S. Y.; Tan, T.; Wang, L.; Lim, R. C.; Lee, H. S.; Lee, S. C.; Goh, B. C. Lack of Association of Single-Nucleotide Polymorphisms in Pregnane X Receptor, Hepatic Nuclear Factor 4alpha, and Constitutive Androstane Receptor With Docetaxel Pharmacokinetics. *Clin. Cancer Res.* **2007**, *13*, 7126–7132.

(28) Dring, M. M.; Goulding, C. A.; Trimble, V. I.; Keegan, D.; Ryan, A. W.; Brophy, K. M.; Smyth, C. M.; Keeling, P. W.; O'Donoghue, D.; O'Sullivan, M.; O'Morain, C.; Mahmud, N.; Wikstrom, A. C.; Kelleher, D.; McManus, R. The Pregnane X Receptor Locus Is Associated With Susceptibility to Inflammatory Bowel Disease. *Gastroenterology* **2006**, *130*, 341–348.

(29) Martinez, A.; Marquez, A.; Mendoza, J.; Taxonera, C.; Fernandez-Arquero, M.; Diaz-Rubio, M.; de la Concha, E. G.; Urcelay, E. Role of the PXR Gene Locus in Inflammatory Bowel Diseases. *Inflammatory Bowel Dis.* **2007**, *13*, 1484–1487.

(30) Sueyoshi, T.; Kawamoto, T.; Zelko, I.; Honkakoski, P.; Negishi, M. The Repressed Nuclear Receptor CAR Responds to Phenobarbital in Activating the Human CYP2B6 Gene. *J. Biol. Chem.* **1999**, *274*, 6043–6046.

(31) Honkakoski, P.; Zelko, I.; Sueyoshi, T.; Negishi, M. The Nuclear Orphan Receptor CAR-Retinoid X Receptor Heterodimer Activates the Phenobarbital-Responsive Enhancer Module of the CYP2B Gene. *Mol. Cell. Biol.* **1998**, *18*, 5652–5658.

(32) Ferguson, S. S.; Chen, Y.; LeCluyse, E. L.; Negishi, M.; Goldstein, J. A. Human CYP2C8 Is Transcriptionally Regulated by the Nuclear Receptors Constitutive Androstane Receptor, Pregnane X Receptor, Glucocorticoid Receptor, and Hepatic Nuclear Factor 4alpha. *Mol. Pharmacol.* **2005**, *68*, 747–757.

(33) Gerbal-Chaloin, S.; Daujat, M.; Pascussi, J. M.; Pichard-Garcia, L.; Vilarem, M. J.; Maurel, P. Transcriptional Regulation of CYP2C9 Gene. Role of Glucocorticoid Receptor and Constitutive Androstane Receptor. *J. Biol. Chem.* **2002**, *277*, 209–217.

(34) Goodwin, B.; Hodgson, E.; D'Costa, D. J.; Robertson, G. R.; Liddle, C. Transcriptional Regulation of the Human CYP3A4 Gene by the Constitutive Androstane Receptor. *Mol. Pharmacol.* **2002**, *62*, 359–365.

(35) Bertilsson, G.; Berkenstam, A.; Blomquist, P. Functionally Conserved Xenobiotic Responsive Enhancer in Cytochrome P450 3A7. *Biochem. Biophys. Res. Commun.* **2001**, *280*, 139–144.

(36) Burk, O.; Arnold, K. A.; Geick, A.; Tegude, H.; Eichelbaum, M. A Role for Constitutive Androstane Receptor in the Regulation of Human Intestinal MDR1 Expression. *Biol. Chem.* **2005**, *386*, 503–513.

(37) Kast, H. R.; Goodwin, B.; Tarr, P. T.; Jones, S. A.; Anisfeld, A. M.; Stoltz, C. M.; Tontonoz, P.; Kliewer, S.; Willson, T. M.; Edwards, P. A. Regulation of Multidrug Resistance-Associated Protein 2 (ABCC2) by the Nuclear Receptors Pregnane X Receptor, Farnesoid X-Activated Receptor, and Constitutive Androstane Receptor. *J. Biol. Chem.* **2002**, *277*, 2908–2915.

(38) Sugatani, J.; Yamakawa, K.; Tonda, E.; Nishitani, S.; Yoshinari, K.; Degawa, M.; Abe, I.; Noguchi, H.; Miwa, M. The Induction of Human UDP-Glucuronosyltransferase 1A1 Mediated Through a Distal Enhancer Module by Flavonoids and Xenobiotics. *Biochem. Pharmacol.* **2004**, *67*, 989–1000.

(39) Blumberg, B.; Sabbagh, W., Jr.; Juguilon, H.; Bolado, J., Jr.; van Meter, C. M.; Ong, E. S.; Evans, R. M. SXR, a Novel Steroid and Xenobiotic-Sensing Nuclear Receptor. *Genes Dev.* **1998**, *12*, 3195–3205.

(40) Waxman, D. J. P450 Gene Induction by Structurally Diverse Xenochemicals: Central Role of Nuclear Receptors CAR, PXR, and PPAR. *Arch. Biochem. Biophys.* **1999**, *369*, 11–23.

(41) Suino, K.; Peng, L.; Reynolds, R.; Li, Y.; Cha, J. Y.; Repa, J. J.; Kliewer, S. A.; Xu, H. E. The Nuclear Xenobiotic Receptor CAR: Structural Determinants of Constitutive Activation and Heterodimerization. *Mol. Cell* **2004**, *16*, 893–905.

(42) Pascussi, J. M.; Drocourt, L.; Gerbal-Chaloin, S.; Fabre, J. M.; Maurel, P.; Vilarem, M. J. Dual Effect of Dexamethasone on CYP3A4 Gene Expression in Human Hepatocytes. Sequential Role of Glucocorticoid Receptor and Pregnane X Receptor. *Eur. J. Biochem.* **2001**, *268*, 6346–6358.

Table 4. Single Nucleotide Polymorphisms Identified in the CAR (*NR1I3*) Gene Locus[a]

		position				allele frequency[c]		
							JP	
dbSNP	location	NT_011512.10	*b*	nucleotide exchange	amino acid exchange	Db	*n* = 253	*n* = 334
rs1063521	Exon 2	4581292	120	A>G	Pro40Pro			
	Exon	4581570	398	T>G			0.002	
rs2307424	Exon 5	4581712	540	C>T	Pro180Pro		0.521	
	Exon 5	4581909	737	A>G	His246Arg			0.004
rs437470	Exon 7	4599629	846	A>G	Pro282Pro	0.347		
	Exon 7	4599829	923	T>C	Leu308Pro			0.002
rs34727960	Exon 7	4599752	969	T>G	Ser323Arg	0.344		0.002
	Exon 7	4599815	1032	G>A	Gln344Gln		0.002	
rs3175551	Exon 7	4599830	1047	T>C	Gly349Gly	0.471		
rs3175822	Exon 7	4599851	1068	A>C	Pro356Pro	0.500		

[a] References provided upon request. [b] From the translational initiation site or from the end of the nearest exon. [c] Db, database; JP, Japanese population.

androstane metabolites such as androstanol (5α-androstan-3α-ol) and androstenol (5α-androstan-16-en-3α-ol).[48,49] Other inhibitors have been identified including clotrimazole and 1-(2-chlorophenylmethylpropyl)-3-isoquinoline-carboxamide.[50,51] CAR has been implicated as a factor in bile acid toxicity,[52,53] thyroid hormone metabolism,[54] glucose homeostasis,[55] and lipid metabolism.[56−58]

As is the case for PXR, nonsynonymous SNPs in CAR are rare (Table 4) and unlikely to be a major contributor to variable transcriptional activation of target genes.

Nevertheless, the nonsynonymous coding SNPs identified so far[59,60] are localized to the ligand binding domain, and considered likely to play a role not only for ligand binding but also for dimerization with RXR, interaction with coactivators, and nuclear localization of the receptor.[61] *In vitro* assays revealed significantly decreased capacity of basal and ligand-dependent transactivation of a CYP3A4 reporter in the presence of the p.His246Arg variant, whereas in cells expressing the p.Leu308Pro variant only the constitutive activity was impaired.[60] Other nonsynonymous CAR variants (p.Val133Gly, p.Ser323Arg) did not modulate CAR activity *in vitro*. It would be expected that individuals harboring the genetic variants would exhibit lower constitutive levels of CAR target genes.[61,62] However, these are rare SNPs.

Members of the OATP1B Subfamily as Key Determinants of Hepatic Drug Uptake

Membrane bound carrier-mediated processes are essential to the cellular uptake and efflux of endogenous and xeno-

(43) Rencurel, F.; Foretz, M.; Kaufmann, M. R.; Stroka, D.; Looser, R.; Leclerc, I.; da, S. X.; Rutter, G. A.; Viollet, B.; Meyer, U. A. Stimulation of AMP-Activated Protein Kinase Is Essential for the Induction of Drug Metabolizing Enzymes by Phenobarbital in Human and Mouse Liver. *Mol. Pharmacol.* **2006**, *70*, 1925–1934.

(44) Koike, C.; Moore, R.; Negishi, M. Extracellular Signal-Regulated Kinase Is an Endogenous Signal Retaining the Nuclear Constitutive Active/Androstane Receptor (CAR) in the Cytoplasm of Mouse Primary Hepatocytes. *Mol. Pharmacol.* **2007**, *71*, 1217–1221.

(45) Yoshinari, K.; Kobayashi, K.; Moore, R.; Kawamoto, T.; Negishi, M. Identification of the Nuclear Receptor CAR:HSP90 Complex in Mouse Liver and Recruitment of Protein Phosphatase 2A in Response to Phenobarbital. *FEBS Lett.* **2003**, *548*, 17–20.

(46) Sueyoshi, T.; Moore, R.; Sugatani, J.; Matsumura, Y.; Negishi, M. PPP1R16A, the Membrane Subunit of Protein Phosphatase 1beta, Signals Nuclear Translocation of the Nuclear Receptor Constitutive Active/Androstane Receptor. *Mol. Pharmacol.* **2008**, *73*, 1113–1121.

(47) Hosseinpour, F.; Timsit, Y.; Koike, C.; Matsui, K.; Yamamoto, Y.; Moore, R.; Negishi, M. Overexpression of the Rho-Guanine Nucleotide Exchange Factor ECT2 Inhibits Nuclear Translocation of Nuclear Receptor CAR in the Mouse Liver. *FEBS Lett.* **2007**, *581*, 4937–4942.

(48) Tzameli, I.; Pissios, P.; Schuetz, E. G.; Moore, D. D. The Xenobiotic Compound 1,4-Bis[2-(3,5-Dichloropyridyloxy)]Benzene Is an Agonist Ligand for the Nuclear Receptor CAR. *Mol. Cell. Biol.* **2000**, *20*, 2951–2958.

(49) Forman, B. M.; Tzameli, I.; Choi, H. S.; Chen, J.; Simha, D.; Seol, W.; Evans, R. M.; Moore, D. D. Androstane Metabolites Bind to and Deactivate the Nuclear Receptor CAR-Beta. *Nature* **1998**, *395*, 612–615.

(50) Moore, L. B.; Parks, D. J.; Jones, S. A.; Bledsoe, R. K.; Consler, T. G.; Stimmel, J. B.; Goodwin, B.; Liddle, C.; Blanchard, S. G.; Willson, T. M.; Collins, J. L.; Kliewer, S. A. Orphan Nuclear Receptors Constitutive Androstane Receptor and Pregnane X Receptor Share Xenobiotic and Steroid Ligands. *J. Biol. Chem.* **2000**, *275*, 15122–15127.

(51) Li, L.; Chen, T.; Stanton, J. D.; Sueyoshi, T.; Negishi, M.; Wang, H. The Peripheral Benzodiazepine Receptor Ligand 1-(2-Chlorophenyl-Methylpropyl)-3-Isoquinoline-Carboxamide Is a Novel Antagonist of Human Constitutive Androstane Receptor. *Mol. Pharmacol.* **2008**, *74*, 443–453.

(52) Guo, G. L.; Lambert, G.; Negishi, M.; Ward, J. M.; Brewer, H. B., Jr.; Kliewer, S. A.; Gonzalez, F. J.; Sinal, C. J. Complementary Roles of Farnesoid X Receptor, Pregnane X Receptor, and Constitutive Androstane Receptor in Protection Against Bile Acid Toxicity. *J. Biol. Chem.* **2003**, *278*, 45062–45071.

(53) Saini, S. P.; Sonoda, J.; Xu, L.; Toma, D.; Uppal, H.; Mu, Y.; Ren, S.; Moore, D. D.; Evans, R. M.; Xie, W. A Novel Constitutive Androstane Receptor-Mediated and CYP3A-Independent Pathway of Bile Acid Detoxification. *Mol. Pharmacol.* **2004**, *65*, 292–300.

(54) Qatanani, M.; Zhang, J.; Moore, D. D. Role of the Constitutive Androstane Receptor in Xenobiotic-Induced Thyroid Hormone Metabolism. *Endocrinology* **2005**, *146*, 995–1002.

biotic compounds. Organic anion transporting polypeptides (OATPs) belong to the solute carrier (SLC) superfamily and are referred to as solute carrier organic anion transporters (SLCOs).[63] Members of the OATP1B subfamily have proven to be important to the hepatic uptake of drugs and hormones due to their localization to the sinusoidal membrane of hepatocytes. In humans, two members of this subfamily, OATP1B1 and OATP1B3, have been identified and noted to have liver-enriched pattern of expression and remarkably broad substrate specificity (Table 6), particularly for many drugs in clinical use.[64−66] In addition, a number of functional SNPs in OATP1B transporters have been noted (Table 7).

OATP1B1 Drug Substrates and Polymorphisms. 3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) exert their cholesterol lowering effect primarily through inhibition of hepatic HMG-CoA reductase. The enhanced hepatic uptake of statins appears to be mediated by OATP1B transporters. *In vitro* studies suggested that OATP1B transporters, especially OATP1B1, are able to mediate the cellular uptake of rosuvastatin,[67] pravastatin,[68,69] atorvastatin,[69] cerivastatin[69] and fluvastatin.[70,71] Although transport of lovastatin has not been directly demonstrated, the significant inhibition of OATP1B mediated cellular uptake suggests that lovastatin may also be a substrate for this transporter.[68,72]

The identification of frequent, naturally occurring single nucleotide polymorphisms of *SLCO1B1* by Tirona and colleagues in 2001[73] and the demonstration of their impact on transport activity proved to be an important milestone that set the stage for determining the *in vivo* relevance of *SLCO1B1* SNPs to drug disposition.[15] A number of variant alleles were identified of which *SLCO1B1*2* (c.217T>C, p.Phe73Leu), *SLCO1B1*3* (c.245T>C and c.467A>G, p.Val82Ala and p.Glu156Gly), *SLCO1B1*5* (c.521T>C, p.Val174Ala), *SLCO1B1*9* (c.1463G>C,

Table 5. Target Genes of CAR and PXR Identified by Promoter Analyses with Identification of Potential Receptor Binding Motifs

target gene	CAR	PXR
CYP3A4	+[30,34]	+[9]
CYP2C9	+[33,155,156]	+[33,155,157]
CYP2C19	+[158]	+[158]
CYP2C8	+[32]	+[32]
CYP2B6	+[30,159,160]	+[159,161]
UGT1A1	+[162,163]	+[162,164]
SULT2A1	+[165]	+[165]
MDR1 (ABCB1)	+[36,166]	+[167,168]
MRP2 (ABCB2)	+[37]	+[37]
MRP4	+[169]	nd[a]
OATP1A2	+[170]	+[170,171]

[a] Not determined.

(55) Moreau, A.; Vilarem, M. J.; Maurel, P.; Pascussi, J. M. Xenoreceptors CAR and PXR Activation and Consequences on Lipid Metabolism, Glucose Homeostasis, and Inflammatory Response. *Mol. Pharmaceutics* **2008**, *5*, 35–41.

(56) Finn, R. D.; Henderson, C. J.; Scott, C. L.; Wolf, C. R. Unsaturated Fatty Acid Regulation of Cytochrome P450 Expression Via a CAR-Dependent Pathway. *Biochem. J.* **2009**, *417*, 43–54.

(57) Masson, D.; Qatanani, M.; Sberna, A. L.; Xiao, R.; Pais de Barros, J. P.; Grober, J.; Deckert, V.; Athias, A.; Gambert, P.; Lagrost, L.; Moore, D. D.; Assem, M. Activation of the Constitutive Androstane Receptor Decreases HDL in Wild-Type and Human ApoA-I Transgenic Mice. *J. Lipid Res.* **2008**, *49*, 1682–1691.

(58) Roth, A.; Looser, R.; Kaufmann, M.; Blattler, S. M.; Rencurel, F.; Huang, W.; Moore, D. D.; Meyer, U. A. Regulatory Cross-Talk Between Drug Metabolism and Lipid Homeostasis: Constitutive Androstane Receptor and Pregnane X Receptor Increase Insig-1 Expression. *Mol. Pharmacol.* **2008**, *73*, 1282–1289.

(59) Ikeda, S.; Kurose, K.; Ozawa, S.; Sai, K.; Hasegawa, R.; Komamura, K.; Ueno, K.; Kamakura, S.; Kitakaze, M.; Tomoike, H.; Nakajima, T.; Matsumoto, K.; Saito, H.; Goto, Y.; Kimura, H.; Katoh, M.; Sugai, K.; Minami, N.; Shirao, K.; Tamura, T.; Yamamoto, N.; Minami, H.; Ohtsu, A.; Yoshida, T.; Saijo, N.; Saito, Y.; Sawada, J. Twenty-Six Novel Single Nucleotide Polymorphisms and Their Frequencies of the NR1I3 (CAR) Gene in a Japanese Population. *Drug Metab. Pharmacokinet.* **2003**, *18*, 413–418.

(60) Ikeda, S.; Kurose, K.; Jinno, H.; Sai, K.; Ozawa, S.; Hasegawa, R.; Komamura, K.; Kotake, T.; Morishita, H.; Kamakura, S.; Kitakaze, M.; Tomoike, H.; Tamura, T.; Yamamoto, N.; Kunitoh, H.; Yamada, Y.; Ohe, Y.; Shimada, Y.; Shirao, K.; Kubota, K.; Minami, H.; Ohtsu, A.; Yoshida, T.; Saijo, N.; Saito, Y.; Sawada, J. Functional Analysis of Four Naturally Occurring Variants of Human Constitutive Androstane Receptor. *Mol. Genet. Metab.* **2005**, *86*, 314–319.

(61) Lamba, J. K. Pharmacogenetics of the Constitutive Androstane Receptor. *Pharmacogenomics* **2008**, *9*, 71–83.

(62) Lamba, J.; Lamba, V.; Schuetz, E. Genetic Variants of PXR (NR1I2) and CAR (NR1I3) and Their Implications in Drug Metabolism and Pharmacogenetics. *Curr. Drug Metab.* **2005**, *6*, 369–383.

(63) Hagenbuch, B.; Meier, P. J. Organic Anion Transporting Polypeptides of the OATP/ SLC21 Family: Phylogenetic Classification As OATP/ SLCO Superfamily, New Nomenclature and Molecular/Functional Properties. *Pfluegers Arch.* **2004**, *447*, 653–665.

(64) Abe, T.; Kakyo, M.; Tokui, T.; Nakagomi, R.; Nishio, T.; Nakai, D.; Nomura, H.; Unno, M.; Suzuki, M.; Naitoh, T.; Matsuno, S.; Yawo, H. Identification of a Novel Gene Family Encoding Human Liver-Specific Organic Anion Transporter LST-1. *J. Biol. Chem.* **1999**, *274*, 17159–17163.

(65) Konig, J.; Cui, Y.; Nies, A. T.; Keppler, D. A Novel Human Organic Anion Transporting Polypeptide Localized to the Basolateral Hepatocyte Membrane. *Am. J. Physiol.* **2000**, *278*, G156–G164.

(66) Abe, T.; Unno, M.; Onogawa, T.; Tokui, T.; Kondo, T. N.; Nakagomi, R.; Adachi, H.; Fujiwara, K.; Okabe, M.; Suzuki, T.; Nunoki, K.; Sato, E.; Kakyo, M.; Nishio, T.; Sugita, J.; Asano, N.; Tanemoto, M.; Seki, M.; Date, F.; Ono, K.; Kondo, Y.; Shiiba, K.; Suzuki, M.; Ohtani, H.; Shimosegawa, T.; Iinuma, K.; Nagura, H.; Ito, S.; Matsuno, S. LST-2, a Human Liver-Specific Organic Anion Transporter, Determines Methotrexate Sensitivity in Gastrointestinal Cancers. *Gastroenterology* **2001**, *120*, 1689–1699.

(67) Ho, R. H.; Tirona, R. G.; Leake, B. F.; Glaeser, H.; Lee, W.; Lemke, C. J.; Wang, Y.; Kim, R. B. Drug and Bile Acid Transporters in Rosuvastatin Hepatic Uptake: Function, Expression, and Pharmacogenetics. *Gastroenterology* **2006**, *130*, 1793–1806.

Table 6. List of Known OATP1B1 and OATP1B3 Substrates

OATP1B1		OATP1B3	
substances	K_m	substances	K_m
	Endogenous Substrates		
cholate	11 μM[172]	cholate	42 μM[173]
taurocholate	10−34 μM[64,172]	taurocholate	6−112 μM[173]
glycocholate	ref 101	glycocholate	43 μM[101]
		taurochendeoxycholate (TCDCA)	ref 173
		taurodeoxycholate (TDCA)	ref 173
		tauroursodeoxycolate (TUDCA)	ref 174
		glucoursodeoxycholate (GUDCA)	ref 174
CDCA-NBD	refs 175, 176	CDCA-NBD	refs 175, 176
thyroxine	3 μM[64]	thyroxine	ref 101
triodothyronine	3 μM[64]	triiodothyronine	6 μM[66,101]
dihydroepiandrosterone 3-sulfate (DHEAS)	22 μM[68,101,172,172]	dihydroepiandrosterone 3-sulfate (DHEAS)	>30[172]
estrone 3-sulfate (E_1S)	0.54−45 μM[172]	estrone 3-sulfate(E_1S)	58 μM
estradiol 17β-glucuronide (E_2G)	4−24 μM[64,65,172,177]	estradiol 17β-glucuronide (E_2G)	5.4−25 μM[172,178,179]
bilirubin	0.1−8 μM[97,172]	bilirubin	39 μM[97]
bisglucuronosyl bilirubin	0.3 μM[172]		
monoglucuronosyl bilirubin	0.1 μM[172]		
leukotriene C_4	ref 64	leukotriene C_4	refs 101, 178
leukotriene E_4	ref 64		
prostaglandin E_2	refs 64, 117		
thromboxane B_2	ref 64		
		CCK-8	4−11 μM[100,179]
	Exogenous Substrates		
ACU154	nd[180]		
		amanitin	4 μM[181]
arsenic (arsenite, arsenate)	nd[182]		
atorvastatin	12.4 μM[68,69,183]		
atrasentan	ref 146	atrasentan	ref 146
Bamet-R2	10 μM[184]		
Bamet-UD2	9.7 μM[184]		
benzylpenicillin	ref 117		
bosentan	44 μM[149,151]	bosentan	141 μM[149,151]
BQ-123	ref 101	BQ-123	ref 101
bromosulfophthalein (BSP)	0.1−0.3 μM[101,172]	bromosulfophthalein (BSP)	0.4−6.0 μM[101,102,178]
caspofungin	ref 185		
cerivastatin	4 μM[186]		
		deltorphin II	ref 101
demethylphalloin	17 μM[187]	demethylphalloin	8 μM[187]
		digoxin	ref 101
		docetaxel	ref 106
		D-[penicillamine[2,5] enkephalin	ref 101
enalapril	262 μM[188]	enalapril	ref 188
		erythromycin	ref 109
ezetimibe-glucuronide	ref 144		
		fexofenadine	108 μM[189]
fluvastatin	1.4−3.5 μM[70,71]	fluvastatin	7 μM[70]
		fluo-3	6.8 μM[190]
methotrexate	39.4 μM[66]	methotrexate	25−39 μM[66]
		microcystin	1.2−9.0 μM[191,192]
olmesartan	13−43 μM[193,194]	olmesartan	44−72 μM[193,194]
		ouabain	ref 101
		paclitaxel	7 μM[106]
phalloidin	17−39 μM[187,195]	phalloidin	8 μM[187]
pitavastatin	3−4 μM[179,196]	pitavastatin	3−4 μM[179,196]
pravastatin	14−34 μM[68,177,197]		
rifampin	2−13 μM[127,128]	rifampin	2 μM[128]
RO 48-5033	60 μM[151]	RO 48-5033	166 μM[151]
rosuvastatin	3 μM[67,198]	rosuvastatin	10 μM[67]
SN-38	ref 94	SN-38	ref 175
S-8921G	1.93 μM[199,200]	S-8921G	1.88 μM[199,200]
temocaprilat	ref 87		
		telmisartan	1 μM[103]
TR-14035	7.5 μM[201]	TR-14035	5.3 μM[201]
troglitazone sulfate	ref 202		
valsartan	1.4 μM[87,203]	valsartan	18 μM[203]

p.Gly488Ala), *SLCO1B1**10 (c.1964A>G, p.Asp655Gly) and *SLCO1B1**12 (c.217T>C and c.1964A>G, p.Phe73Leu and p.Asp655Gly) exhibited reduced transport activity for endogenous compounds such as estrone 3-sulfate or estradiol 17β-glucuronide. Most of the variants associated with loss of activity were noted to be rare, but one variant (c.521T>C, p.Val174Ala) was noted to be relatively common. A comprehensive list of currently known genetic polymorphisms in the *SLCO1B1* is summarized in Tables 7 and 8.

Subsequently *SLCO1B1* variants have been shown to influence the pharmacokinetic profiles of several substrate drugs, including pravastatin,[74−77] pitavastatin,[78,79] simvas-

Table 7. Single Nucleotide Polymorphisms Identified in the SLCO1B1 Gene Locus[a]

		position				allele frequency[c]				
						EA	AA	JP		FP
dbSNP	location	NT_009714.16	*b*	nucleotide exchange	amino acid exchange	*n* = 49	*n* = 22	*n* = 354	*n* = 120	*n* = 38
rs4149015	5′-flanking	14042296	−11187	G>A				0.153		0.146
	5′-flanking	14042373	−11110	T>G						0.02
	5′-flanking	14042494	−10989	G>A				0.076		
	5′-flanking	14042530	−10953	A>T				0.003		
	5′-flanking	14042793	−10690	T>C				0.076		
	5′-flanking	14042860	−10623	A/Adel				0.003		
	5′-flanking	14042984	−10499	A>C						0.085
	5′-flanking	14043018	−10465	T>C				0.003		
	Intron 1	14043209	IVS1+65	G>C				0.014		
rs2010668	Intron 1	14053267	IVS1−155	G>T				0.113		
	5′UTR	14053480	−3	A>C				0.014		
rs11557087	Exon 2	14053510	123	A>G	Ala10Thr					
	Intron 2	14053635	IVS2+69	T>C				0.003		
	Intron 2	14053648	IVS2+82	C>T				0.003		
	Intron 2	14053734	IVS2+168	T>C				0.008		
rs4149021	Intron 2	14053759	IVS2+193	G>A				0.153		0.095
	Intron 2	14053769	IVS2+203	A>T				0.003		0.065
	Intron 2	14053807	IVS2+241	T>C				0.006		
rs12303784	Intron 2	14053814	IVS2+248	A>G				0.003		
	Intron 2	14084429	IVS2−129	A>G				0.003		
	Intron 2	14084478	IVS2−80	T>C				0.008		
rs56101265	Exon 3	14084690	218	T>C	Phe73Leu	0.02	0.00		0.00	
rs2291073	Intron 3	14084788	IVS3+89	T>G				0.271	0.00	
rs2291074	Intron 3	14084923	IVS3+224	A>G				0.243		
rs56061388	Exon 4	14086503	245	T>C	Val82Ala	0.02	0.00			
	Exon 4	14086569	311	T>A	Met104Lys			0.003		
rs4149036	Intron 4	14086714	IVS4+97	C>A				0.427		
	Intron 4	14088523	IVS4−161	T>C				0.017		
rs2306283	Exon 5	14088712	388	A>G	Asn130Asp	0.30	0.74	0.667	0.63	0.447
	Exon 5		411	G>A	Ser137Ser					0.065
rs2306282	Exon 5	14088776	452	A>G	Asn151Ser			0.034	0.04	
	Exon 5		463	C>A	Pro155Thr	0.16	0.02		0.00	0.065
	Exon 5		467	A>G	Glu156Gly	0.02	0.00		0.00	
	Intron 5		IVS5+160	C>T						0.065
rs4149044	Intron 5	14088970	IVS5+165	A>T				0.427		0.342
rs4149045	Intron 5	14088994	IVS5+189	G>A				0.429		0.276
rs414904	Intron 5	14088996	IVS5+191	G>A				0.331		0.421
rs4149096	Intron 5	14090372−14090377	IVS5−107_112	delCTTGTA				0.427		0.447
	Intron 5	14090469	IVS5−15	C>G				0.003		
	Exon 6	14090511	509	T>C	Met170Thr			0.003		
rs4149056	Exon 6	14090523	521	T>C	Val174Ala	0.14	0.02	0.175	0.16	0.197
rs4149057	Exon 6	14090573	571	T>C	Leu191Leu			0.333		0.552
	Exon 6	14090578	576	G>A	Gly192Gly			0.003		
	Exon 6	14090580	578	T>G	Leu193Arg	0.003[d,d]				0.000
rs2291075	Exon 6	14090599	597	C>T	Phe199Phe			0.427		0.447
	Exon 6	14090603	601	A>G	Lys201Glu			0.003		
rs4603354	Exon 6	14090610	608	G>A	Glu203Gly					
rs2291076	Intron 7	14090961	IVS7+33	C>T				0.336		0.474
rs11045852	Exon 8	14108859	733	A>G	Val245Ile					
rs11045853	Exon 8	14108884	758	G>A	Gln253Arg					
rs11045854	Exon 8	14109008	882	G>A	Leu294Leu					
	Exon 9	14112452	1007	C>G	Pro336Arg			0.006	0.01	
rs55901008	Exon 9	14112503	1058	T>C	Ile353Thr	0.02	0.00		0.00	
rs57040246	Exon 9	14112531	1086	C>T	Tyr362Tyr					
	Intron 9	14114331	IVS9−68	G>C				0.003		
	Intron 10	14114309	IVS10−128	delA						0.079
rs4149099	Intron 10	14117669−14117670	IVS10−106_107	insCTT				0.647		0.500
	Intron 10	14117728−14117730	IVS10−46_48	delTTT				0.003		
rs59113707	Exon 10	14114463	1200	C>A	Phe400Leu					
rs11045859	Exon 10	14114511	1248	G>A	Val416Val					
rs61176925	Exon 10	14114535	1272	A>C	Leu424Phe					
rs56387224	Exon 10	14114557	1294	A>G	Asn432Asp	0.01	0.00		0.00	
	Exon 11	14117829	1385	A>G	Asp462Gly	0.01	0.00		0.00	
rs59502379	Exon 11	14117907	1463	G>C	Gly488Ala	0.00	0.09		0.00	
rs4149070	Intron 11	14128857	IVS11−170	C>G				0.280		0.131
rs4149071	Intron 11	14128938	IVS11−89	T>C				0.280		0.131
rs4149100	Intron 11	14128952	IVS11−75	delA				0.395		0.316
rs4149072	Intron 11	14128959	IVS11−68	G>A				0.280		0.053
	Intron 11	14129015	IVS11−12	A>G				0.014		
	Exon 12	14129082	1553	T>C	Ser518Leu			0.003		
	Exon 12	14129158	1628	T>G	Leu543Trp				<0.01[d]	
rs987839	Intron 12	14133812	IVS12−396	G>A				0.316		

Table 7. Continued

		position				allele frequency[c]				
						EA	AA	JP		FP
dbSNP	location	NT_009714.16	*b*	nucleotide exchange	amino acid exchange	*n* = 49	*n* = 22	*n* = 354	*n* = 120	*n* = 38
	Intron 12	14134097	IVS12−111	C>T				0.020		
	Intron 12	14134207	IVS12−1	G>T				0.003		
	Exon 13	14134263	1738	T>C	Arg580Stop			0.008		
	Intron 12	14134270	IVS+9	A>G						0.092
rs4149080	Intron 13	14136533	IVS13−97	G>C				0.395		0.079
	Intron 13	14136595	IVS13−159	G>C						0.316
	Intron 14	14136797	IVS14+50	T>G				0.011		
	Intron 14	14150655	IVS14−232	G>A				0.006		
	Intron 14	14150656	IVS14−231	T>C				0.251		
rs34671512	Exon 15	14150950	1929	A/C	Leu643Phe					0.171
rs56199088	Exon 15	14150985	1964	A>G	Asp655Gly	0.02	0.00		0.00	
	Exon 15	14151004	1983	T>C	Asn661Asn			0.006	0.00	
rs55737008	Exon 15	14151021	2000	A>G	Glu667Gly	0.02	0.34			
	3′-UTR	14151137	2116(*40)c	C>G				0.011		
rs4149085	3′-UTR	14151264	2243(*167)c	T>C				0.251		
rs4149086	3′-UTR	14151425	2404(*328)c	A>G				0.025		
rs4149087	3′-UTR	14151536	2515(*439)c	G>T				0.333		
rs4149088	3′-UTR	14151560	2539 (*463)c	G>A				0.333		

[a] References provided upon request. [b] From the translational initiation site or from the end of the nearest exon. [c] EA, European Americans; AA, African Americans; JP, Japanese population; FP, Finnish population. [d] Identified in 2 Japanese patients with statin induced myopathy.

Table 8. *SLCO1B1* Haplotypes and Frequencies[a]

		frequencies[b]	
alleles	polymorphism or haplotype	JP	FP
SLCO1B1 *1a		0.352−0.325	0.07
SLCO1B1 *1b	388A>G	0.537−0.480	
SLCO1B1 *1c	455G>A, 721G>A		
SLCO1B1 *2	217T>C		
SLCO1B1 *3	245T>C, 467A>G		
SLCO1B1 *4	463C>A		
SLCO1B1 *5	521T>C	0.007−0.000	0.010
SLCO1B1 *6	1058T>C		
SLCO1B1 *7	1294A>G		
SLCO1B1 *8	1385A>G		
SLCO1B1 *9	1463G>C		
SLCO1B1 *10	1964A>G		
SLCO1B1 *11	2000A>G		
SLCO1B1 *12	217T>C, 1964A>G		
SLCO1B1 *13	245T>C, 467A>G, 2000A>G		
SLCO1B1 *14	388A>G, 463C>A		
SLCO1B1 *15	388A>G, 512T>C	0.103−0.150	
SLCO1B1 *15B	388A>G, (IVS5 + 165A>T), (IVS5 + 189G>A), (IVS5−107_112delCTTGTA), 521T>C, 597C>T		0.05
SLCO1B1 *16	452A>G	0.038	0.09
SLCO1B1 *17	−11187G>A, 388A>G, 521T>C		0.04
SLCO1B1 *18	388A>G, (411G>A), 463C>A, (571T>C), 578T>G		0.07
SLCO1B1 *19	388A>G, (597C>T), 1929A>C		0.01
SLCO1B1 *20	388A>G, (597C>T), 1929A>C		0.04
SLCO1B1 *21	−11187G>A, 388A>G, (597C>T), 1929A>C		0.04

[a] References provided upon request. [b] JP, Japanese population; FP, Finnish population.

tatin,[80] torasemid,[81] repaglinide,[82,83] fexofenadine[84] and atorvastatin.[85,86] Subjects harboring the *SLCO1B1**15 allele (c.388A>G and c.521T>C) exhibited elevated systemic exposure to pravastatin as compared to subjects who possess the wild-type allele.[75,76] In contrast, several studies suggest that the *SLCO1B1**1b allele (c.388A>G) may have enhanced transport activity as compared to the wild-type allele (*SLCO1B1**1a allele).[74,77,87] Similar results have been shown for the novel antidiabetic agent nateglinide.[88] In the case of statins the major route of elimination and their pharmacological target is the liver. Therefore it is not surprising that the risk for adverse events, such as those affecting skeletal

muscle, would be greater when the hepatic uptake of statins is reduced due to the presence of reduced-function OATP1B1 variants. Indeed, this is fully consistent with recent findings which show that individuals carrying the impaired-function alleles are at a higher risk for statin-induced myopathy and rhabdomyolysis.[89−91] However studies of OATP1B1 variants as a determinant of statin efficacy, in terms of their lipid lowering effects, have not been consistent.[92,93]

(68) Hsiang, B.; Zhu, Y.; Wang, Z.; Wu, Y.; Sasseville, V.; Yang, W. P.; Kirchgessner, T. G. A Novel Human Hepatic Organic Anion Transporting Polypeptide (OATP2). Identification of a Liver-Specific Human Organic Anion Transporting Polypeptide and Identification of Rat and Human Hydroxymethylglutaryl-CoA Reductase Inhibitor Transporters. *J. Biol. Chem.* **1999**, *274*, 37161–37168.

(69) Kameyama, Y.; Yamashita, K.; Kobayashi, K.; Hosokawa, M.; Chiba, K. Functional Characterization of SLCO1B1 (OATP-C) Variants, SLCO1B1*5, SLCO1B1*15 and SLCO1B1*15+C1007G, by Using Transient Expression Systems of HeLa and HEK293 Cells. *Pharmacogenet. Genomics* **2005**, *15*, 513–522.

(70) Kopplow, K.; Letschert, K.; Konig, J.; Walter, B.; Keppler, D. Human Hepatobiliary Transport of Organic Anions Analyzed by Quadruple-Transfected Cells. *Mol. Pharmacol.* **2005**, *68*, 1031–1038.

(71) Noe, J.; Portmann, R.; Brun, M. E.; Funk, C. Substrate-Dependent Drug-Drug Interactions Between Gemfibrozil, Fluvastatin and Other Organic Anion-Transporting Peptide (OATP) Substrates on OATP1B1, OATP2B1, and OATP1B3. *Drug Metab. Dispos.* **2007**, *35*, 1308–1314.

(72) Chen, C.; Mireles, R. J.; Campbell, S. D.; Lin, J.; Mills, J. B.; Xu, J. J.; Smolarek, T. A. Differential Interaction of 3-Hydroxy-3-Methylglutaryl-Coa Reductase Inhibitors With ABCB1, ABCC2, and OATP1B1. *Drug Metab. Dispos.* **2005**, *33*, 537–546.

(73) Tirona, R. G.; Leake, B. F.; Merino, G.; Kim, R. B. Polymorphisms in OATP-C: Identification of Multiple Allelic Variants Associated With Altered Transport Activity Among European- and African-Americans. *J. Biol. Chem.* **2001**, *276*, 35669–35675.

(74) Ho, R. H.; Choi, L.; Lee, W.; Mayo, G.; Schwarz, U. I.; Tirona, R. G.; Bailey, D. G.; Michael, S. C.; Kim, R. B. Effect of Drug Transporter Genotypes on Pravastatin Disposition in European- and African-American Participants. *Pharmacogenet. Genomics* **2007**, *17*, 647–656.

(75) Nishizato, Y.; Ieiri, I.; Suzuki, H.; Kimura, M.; Kawabata, K.; Hirota, T.; Takane, H.; Irie, S.; Kusuhara, H.; Urasaki, Y.; Urae, A.; Higuchi, S.; Otsubo, K.; Sugiyama, Y. Polymorphisms of OATP-C (SLC21A6) and OAT3 (SLC22A8) Genes: Consequences for Pravastatin Pharmacokinetics. *Clin. Pharmacol. Ther.* **2003**, *73*, 554–565.

(76) Niemi, M.; Schaeffeler, E.; Lang, T.; Fromm, M. F.; Neuvonen, M.; Kyrklund, C.; Backman, J. T.; Kerb, R.; Schwab, M.; Neuvonen, P. J.; Eichelbaum, M.; Kivisto, K. T. High Plasma Pravastatin Concentrations Are Associated With Single Nucleotide Polymorphisms and Haplotypes of Organic Anion Transporting Polypeptide-C (OATP-C, SLCO1B1). *Pharmacogenetics* **2004**, *14*, 429–440.

(77) Mwinyi, J.; Johne, A.; Bauer, S.; Roots, I.; Gerloff, T. Evidence for Inverse Effects of OATP-C (SLC21A6) 5 and 1b Haplotypes on Pravastatin Kinetics. *Clin. Pharmacol. Ther.* **2004**, *75*, 415–421.

(78) Chung, J. Y.; Cho, J. Y.; Yu, K. S.; Kim, J. R.; Oh, D. S.; Jung, H. R.; Lim, K. S.; Moon, K. H.; Shin, S. G.; Jang, I. J. Effect of OATP1B1 (SLCO1B1) Variant Alleles on the Pharmacokinetics of Pitavastatin in Healthy Volunteers. *Clin. Pharmacol. Ther.* **2005**, *78*, 342–350.

(79) Ieiri, I.; Suwannakul, S.; Maeda, K.; Uchimaru, H.; Hashimoto, K.; Kimura, M.; Fujino, H.; Hirano, M.; Kusuhara, H.; Irie, S.; Higuchi, S.; Sugiyama, Y. SLCO1B1 (OATP1B1, an Uptake Transporter) and ABCG2 (BCRP, an Efflux Transporter) Variant Alleles and Pharmacokinetics of Pitavastatin in Healthy Volunteers. *Clin. Pharmacol. Ther.* **2007**, *82*, 541–547.

(80) Pasanen, M. K.; Neuvonen, M.; Neuvonen, P. J.; Niemi, M. SLCO1B1 Polymorphism Markedly Affects the Pharmacokinetics of Simvastatin Acid. *Pharmacogenet. Genomics* **2006**, *16*, 873–879.

(81) Werner, D.; Werner, U.; Meybaum, A.; Schmidt, B.; Umbreen, S.; Grosch, A.; Lestin, H. G.; Graf, B.; Zolk, O.; Fromm, M. F. Determinants of Steady-State Torasemide Pharmacokinetics: Impact of Pharmacogenetic Factors, Gender and Angiotensin II Receptor Blockers. *Clin. Pharmacokinet.* **2008**, *47*, 323–332.

(82) Niemi, M.; Backman, J. T.; Kajosaari, L. I.; Leathart, J. B.; Neuvonen, M.; Daly, A. K.; Eichelbaum, M.; Kivisto, K. T.; Neuvonen, P. J. Polymorphic Organic Anion Transporting Polypeptide 1B1 Is a Major Determinant of Repaglinide Pharmacokinetics. *Clin. Pharmacol. Ther.* **2005**, *77*, 468–478.

(83) Kalliokoski, A.; Neuvonen, M.; Neuvonen, P. J.; Niemi, M. The Effect of SLCO1B1 Polymorphism on Repaglinide Pharmacokinetics Persists Over a Wide Dose Range. *Br. J. Clin. Pharmacol.* **2008**, *66*, 818–825.

(84) Niemi, M.; Kivisto, K. T.; Hofmann, U.; Schwab, M.; Eichelbaum, M.; Fromm, M. F. Fexofenadine Pharmacokinetics Are Associated With a Polymorphism of the SLCO1B1 Gene (Encoding OATP1B1). *Br. J. Clin. Pharmacol.* **2005**, *59*, 602–604.

(85) Kalliokoski, A.; Backman, J.; Kurkinen, K.; Neuvonen, P., Niemi M. Effects of Gemfibrozil and Atorvastatin on the Pharmacokinetics of Repaglinide in Relation to SLCO1B1 Polymorphism. *Clin. Pharmacol. Ther.* **2008**, PMID: 18418370.

(86) Pasanen, M. K.; Fredrikson, H.; Neuvonen, P. J.; Niemi, M. Different Effects of SLCO1B1 Polymorphism on the Pharmacokinetics of Atorvastatin and Rosuvastatin. *Clin. Pharmacol. Ther.* **2007**, *82*, 726–733.

(87) Maeda, K.; Ieiri, I.; Yasuda, K.; Fujino, A.; Fujiwara, H.; Otsubo, K.; Hirano, M.; Watanabe, T.; Kitamura, Y.; Kusuhara, H.; Sugiyama, Y. Effects of Organic Anion Transporting Polypeptide 1B1 Haplotype on Pharmacokinetics of Pravastatin, Valsartan, and Temocapril. *Clin. Pharmacol. Ther.* **2006**, *79*, 427–439.

(88) Zhang, W.; He, Y. J.; Han, C. T.; Liu, Z. Q.; Li, Q.; Fan, L.; Tan, Z. R.; Zhang, W. X.; Yu, B. N.; Wang, D.; Hu, D. L.; Zhou, H. H. Effect of SLCO1B1 Genetic Polymorphism on the Pharmacokinetics of Nateglinide. *Br. J. Clin. Pharmacol.* **2006**, *62*, 567–572.

(89) Link, E.; Parish, S.; Armitage, J.; Bowman, L.; Heath, S.; Matsuda, F.; Gut, I.; Lathrop, M.; Collins, R. SLCO1B1 Variants and Statin-Induced Myopathy—a Genomewide Study. *N. Engl. J. Med.* **2008**, *359*, 789–799.

(90) Furihata, T.; Satoh, N.; Ohishi, T.; Ugajin, M.; Kameyama, Y.; Morimoto, K.; Matsumoto, S.; Yamashita, K.; Kobayashi, K.; Chiba, K. Functional Analysis of a Mutation in the SLCO1B1 Gene (c.1628T>G) Identified in a Japanese Patient With Pravastatin-Induced Myopathy. *Pharmacogenomics J.* **2009**, *9*, 185–193.

(91) Morimoto, K.; Oishi, T.; Ueda, S.; Ueda, M.; Hosokawa, M.; Chiba, K. A Novel Variant Allele of OATP-C (SLCO1B1) Found in a Japanese Patient With Pravastatin-Induced Myopathy. *Drug Metab. Pharmacokinet.* **2004**, *19*, 453–455.

Table 9. Single Nucleotide Polymorphisms Identified in the SLCO1B3 Gene Locus[a]

		position				allele frequency[c]		
dbSNP	location	NT_009714.16	*b*	nucleotide exchange	amino acid exchange	EA[d] ($n = 92$)	EP ($n = 182$)	EA ($n = 119$)
rs61612406	Exon 2	13727657	10	A>G	Arg4His			
rs57325543	Exon 3	13767005	154	A>G	Val52Ile			
rs4149117	Exon 4	13770454	334	*T*>G	Ser112Ala	0.853	0.780	0.820
rs57585902	Exon 5	13773004	439	A>G	Thr147Ala	0.005		0.980
rs7311358	Exon 7	13774734	699	G>A	Met233Ile	0.841	0.710	0.200
rs60140950	Exon 8	13787182	767	G>C	Gly256Ala	0.189		0.170
rs61673910	Exon 10	13791517	1309	G>A	Gly437Ser			
	Exon 12	13795387	1559	A>C	His520Pro	0.00		0.00
	Exon 12	13795391	1564	G>T	Gly522Cys		0.019	
rs12299012	Exon 12	13795507	1679	T>C	Val560Ala	0.016		0.003

[a] References provided upon request. [b] From the translational initiation site or from the end of the nearest exon. [c] EA, European Americans; EP, European population. [d] 92 cancer patients with different cancer entities 27% breast cancer, 26% prostate cancer, 12% lung cancer.

OATP1B1 also appears to play a role in the hepatic uptake of anticancer drugs, such as SN-38,[94] a drug widely used to treat colon cancer. Most studies to date have focused on the role of the promoter polymorphism in the drug conjugating enzyme UGT1A1 as the main determinant of unexpected toxicity from SN-38 therapy. However, the observed toxicities may be the result of synergistic or additive effects of low metabolic (*UGT1A1**6/*28) and transport (*SLCO1B1**15/*15) capabilities.[95] In addition to drugs, it is interesting to note that recent reports indicate that OATP1B1 may also play a role in the regulation of cholesterol synthesis. In fact the common *SLCO1B1* genotype *SCLO1B1*1b/*1b* was associated with an increased cholesterol synthesis rate as characterized by the higher plasma desmosterol to cholesterol ratio and elevated plasma desmosterol concentration in individuals harboring this OATP1B1 variant.[96] Desmosterol is a late intermediate in the cholesterol synthesis pathway and a well-established indicator of the rate of cholesterol synthesis.

OATP1B3 Drug Substrates and Polymorphisms. OATP1B3 is the second member of the OATP1B subfamily, and although noted to have a liver enriched pattern of expression, however this transporter has also been detected in other tissues including the placenta,[97] prostate[98] and colon.[99] OATP1B3 shares a variety of substrates with OATP1B1, but in most cases with lower affinity (Table 6). Only a few substrates have been shown to be exclusively transported by OATP1B3 such as the gastrointestinal peptide hormone CCK-8[100] and the cardiac glycoside digoxin.[101] Similar to OATP1B1, several naturally occurring SNPs have been identified in *SLCO1B3* gene. Specifically, c.T334T>G (p.Ser112Ala) and c.699G>A (p.Met233Ile) have been shown to occur with relative high allele frequencies (Table 9). However *in vitro* assessments of such SNPs in terms of transport activity have been inconclusive.[102] Similarly, the *in vivo* relevance of those SNPs has also been variable or not significant. Studies that looked at the role of OATP1B3 variants on the pharmacokinetic parameters of telmisartan, a drug thought to be a substrate of only OATP1B3 and not OATP1B1, did not reveal any differences in exposure or clearance of the compound.[103−105] Similar results were seen for paclitaxel and docetaxel,[106−108] suggesting that OATP1B3 variants play a minor role in observed

(92) Zhang, W.; Chen, B. L.; Ozdemir, V.; He, Y. J.; Zhou, G.; Peng, D. D.; Deng, S.; Xie, Q. Y.; Xie, W.; Xu, L. Y.; Wang, L. C.; Fan, L.; Wang, A.; Zhou, H. H. SLCO1B1 521T-->C Functional Genetic Polymorphism and Lipid-Lowering Efficacy of Multiple-Dose Pravastatin in Chinese Coronary Heart Disease Patients. *Br. J. Clin. Pharmacol.* **2007**, *64*, 346–352.

(93) Couvert, P.; Giral, P.; Dejager, S.; Gu, J.; Huby, T.; Chapman, M. J.; Bruckert, E.; Carrie, A. Association Between a Frequent Allele of the Gene Encoding OATP1B1 and Enhanced LDL-Lowering Response to Fluvastatin Therapy. *Pharmacogenomics* **2008**, *9*, 1217–1227.

(94) Nozawa, T.; Minami, H.; Sugiura, S.; Tsuji, A.; Tamai, I. Role of Organic Anion Transporter OATP1B1 (OATP-C) in Hepatic Uptake of Irinotecan and Its Active Metabolite, 7-Ethyl-10-Hydroxycamptothecin: in Vitro Evidence and Effect of Single Nucleotide Polymorphisms. *Drug Metab. Dispos.* **2005**, *33*, 434–439.

(95) Takane, H.; Kawamoto, K.; Sasaki, T.; Moriki, K.; Moriki, K.; Kitano, H.; Higuchi, S.; Otsubo, K.; Ieiri, I. Life-Threatening Toxicities in a Patient With UGT1A1*6/*28 and SLCO1B1*15/*15 Genotypes After Irinotecan-Based Chemotherapy. *Cancer Chemother. Pharmacol.* **2009**, *63*, 1165–1169.

(96) Pasanen, M. K.; Miettinen, T. A.; Gylling, H.; Neuvonen, P. J.; Niemi, M. Polymorphism of the Hepatic Influx Transporter Organic Anion Transporting Polypeptide 1B1 Is Associated With Increased Cholesterol Synthesis Rate. *Pharmacogenet. Genomics* **2008**, *18*, 921–926.

(97) Briz, O.; Serrano, M. A.; MacIas, R. I.; Gonzalez-Gallego, J.; Marin, J. J. Role of Organic Anion-Transporting Polypeptides, OATP-A, OATP-C and OATP-8, in the Human Placenta-Maternal Liver Tandem Excretory Pathway for Foetal Bilirubin. *Biochem. J.* **2003**, *371*, 897–905.

(98) Hamada, A.; Sissung, T.; Price, D. K.; Danesi, R.; Chau, C. H.; Sharifi, N.; Venzon, D.; Maeda, K.; Nagao, K.; Sparreboom, A.; Mitsuya, H.; Dahut, W. L.; Figg, W. D. Effect of SLCO1B3 Haplotype on Testosterone Transport and Clinical Outcome in Caucasian Patients With Androgen-Independent Prostatic Cancer. *Clin. Cancer Res.* **2008**, *14*, 3312–3318.

(99) Ballestero, M. R.; Monte, M. J.; Briz, O.; Jimenez, F.; Gonzalez-San Martin, F.; Marin, J. J. Expression of Transporters Potentially Involved in the Targeting of Cytostatic Bile Acid Derivatives to Colon Cancer and Polyps. *Biochem. Pharmacol.* **2006**, *72*, 729–738.

interindividual variability of its substrate drugs. Recently OATP1B3 was shown to impact hepatic accumulation of erythromycin as assessed using the erythromycin breath test (ERMBT). This was unexpected given that the erythromycin breath test has been used as a marker of hepatic CYP3A4 activity. Franke et al. were able to show that individuals carrying two copies of the T allele at the 334 locus had a 2.4-fold lower value for ERMBT $1/T(\max)$, suggesting a more rapid hepatic uptake.[109] However recent findings in prostate cancer patients suggest lower transport activity of the c.334T>G variant of OATP1B3 for testosterone. OATP1B3 seems to be exclusively expressed in prostate cancer, and the linked OATP1B3 variants c.334T>G and c.688G>A have been demonstrated to be associated with lower transport activity for testosterone, and thought to be a positive prognostic factor for this tumor entity.[98,110]

OATP2B1 Drug Substrates and Polymorphisms. OATP2B1 is the only member of the human OATP2B subfamily of solute carriers.[111] In contrast to members of the OATP1B subfamily, substrate specificity for OATP2B1 is much more restricted, although it is more ubiquitously expressed. In fact, OATP2B1 has been shown to be expressed in small intestine, colon, liver, pancreas, heart, testis, mammary gland, platelets, and placenta.[112−117] Recent findings suggest that OATP2B1 might be involved in the disposition of the oral renin-inhibitor aliskiren ($K_m = 72\ \mu M$).[118] In addition, OATP2B1 has been implicated in the transport of atorvastatin ($K_m = 0.2\ \mu M$),[114] amidarone,[119] rosuvastatin ($K_m = 2-6\ \mu M$),[67,120] fluvas-

(100) Ismair, M. G.; Stieger, B.; Cattori, V.; Hagenbuch, B.; Fried, M.; Meier, P. J.; Kullak-Ublick, G. A. Hepatic Uptake of Cholecystokinin Octapeptide by Organic Anion-Transporting Polypeptides OATP4 and OATP8 of Rat and Human Liver. *Gastroenterology* **2001**, *121*, 1185–1190.

(101) Kullak-Ublick, G. A.; Ismair, M. G.; Stieger, B.; Landmann, L.; Huber, R.; Pizzagalli, F.; Fattinger, K.; Meier, P. J.; Hagenbuch, B. Organic Anion-Transporting Polypeptide B (OATP-B) and Its Functional Comparison With Three Other OATPs of Human Liver. *Gastroenterology* **2001**, *120*, 525–533.

(102) Letschert, K.; Keppler, D.; Konig, J. Mutations in the SLCO1B3 Gene Affecting the Substrate Specificity of the Hepatocellular Uptake Transporter OATP1B3 (OATP8). *Pharmacogenetics* **2004**, *14*, 441–452.

(103) Ishiguro, N.; Maeda, K.; Kishimoto, W.; Saito, A.; Harada, A.; Ebner, T.; Roth, W.; Igarashi, T.; Sugiyama, Y. Predominant Contribution of OATP1B3 to the Hepatic Uptake of Telmisartan, an Angiotensin II Receptor Antagonist, in Humans. *Drug Metab. Dispos.* **2006**, *34*, 1109–1115.

(104) Ishiguro, N.; Maeda, K.; Saito, A.; Kishimoto, W.; Matsushima, S.; Ebner, T.; Roth, W.; Igarashi, T.; Sugiyama, Y. Establishment of a Set of Double Transfectants Coexpressing Organic Anion Transporting Polypeptide 1B3 and Hepatic Efflux Transporters for the Characterization of the Hepatobiliary Transport of Telmisartan Acylglucuronide. *Drug Metab. Dispos.* **2008**, *36*, 796–805.

(105) Miura, M.; Satoh, S.; Inoue, K.; Saito, M.; Habuchi, T.; Suzuki, T. Telmisartan Pharmacokinetics in Japanese Renal Transplant Recipients. *Clin. Chim. Acta* **2009**, *399*, 83–87.

(106) Smith, N. F.; Acharya, M. R.; Desai, N.; Figg, W. D.; Sparreboom, A. Identification of OATP1B3 As a High-Affinity Hepatocellular Transporter of Paclitaxel. *Cancer Biol. Ther.* **2005**, *4*, 815–818.

(107) Smith, N. F.; Marsh, S.; Scott-Horton, T. J.; Hamada, A.; Mielke, S.; Mross, K.; Figg, W. D.; Verweij, J.; McLeod, H. L.; Sparreboom, A. Variants in the SLCO1B3 Gene: Interethnic Distribution and Association With Paclitaxel Pharmacokinetics. *Clin. Pharmacol. Ther.* **2007**, *81*, 76–82.

(108) Baker, S.; Verweij, J.; Cusatis, G.; van Schaik, R.; Marsh, S.; Orwick, S.; Franke, R.; Hu, S.; Schuetz, E.; Lamba, V.; Messersmith, W.; Wolff, A.; Carducci, M.; Sparreboom, A. Pharmacogenetic Pathway Analysis of Docetaxel Elimination. *Clin. Pharmacol. Ther.* **2009**, *85*, 155–163.

(109) Franke, R. M.; Baker, S. D.; Mathijssen, R. H.; Schuetz, E. G.; Sparreboom, A. Influence of Solute Carriers on the Pharmacokinetics of CYP3A4 Probes. *Clin. Pharmacol. Ther.* **2008**, *84*, 704–709.

(110) Sharifi, N.; Hamada, A.; Sissung, T.; Danesi, R.; Venzon, D.; Baum, C.; Gulley, J. L.; Price, D. K.; Dahut, W. L.; Figg, W. D. A Polymorphism in a Transporter of Testosterone Is a Determinant of Androgen Independence in Prostate Cancer. *BJU Int.* **2008**, *102*, 617–621.

(111) Hagenbuch, B.; Gui, C. Xenobiotic Transporters of the Human Organic Anion Transporting Polypeptides (OATP) Family. *Xenobiotica* **2008**, *38*, 778–801.

(112) Nozawa, T.; Nakajima, M.; Tamai, I.; Noda, K.; Nezu, J.; Sai, Y.; Tsuji, A.; Yokoi, T. Genetic Polymorphisms of Human Organic Anion Transporters OATP-C (SLC21A6) and OATP-B (SLC21A9): Allele Frequencies in the Japanese Population and Functional Analysis. *J. Pharmacol. Exp. Ther.* **2002**, *302*, 804–813.

(113) Tamai, I.; Nozawa, T.; Koshida, M.; Nezu, J.; Sai, Y.; Tsuji, A. Functional Characterization of Human Organic Anion Transporting Polypeptide B (OATP-B) in Comparison With Liver-Specific OATP-C. *Pharm. Res.* **2001**, *18*, 1262–1269.

(114) Grube, M.; Kock, K.; Oswald, S.; Draber, K.; Meissner, K.; Eckel, L.; Bohm, M.; Felix, S. B.; Vogelgesang, S.; Jedlitschky, G.; Siegmund, W.; Warzok, R.; Kroemer, H. K. Organic Anion Transporting Polypeptide 2B1 Is a High-Affinity Transporter for Atorvastatin and Is Expressed in the Human Heart. *Clin. Pharmacol. Ther.* **2006**, *80*, 607–620.

(115) Grube, M.; Reuther, S.; Meyer Zu, S. H.; Kock, K.; Draber, K.; Ritter, C. A.; Fusch, C.; Jedlitschky, G.; Kroemer, H. K. Organic Anion Transporting Polypeptide 2B1 and Breast Cancer Resistance Protein Interact in the Transepithelial Transport of Steroid Sulfates in Human Placenta. *Drug Metab. Dispos.* **2007**, *35*, 30–35.

(116) Niessen, J.; Jedlitschky, G.; Grube, M.; Bien, S.; Schwertz, H.; Ohtsuki, S.; Kawakami, H.; Kamiie, J.; Oswald, S.; Starke, K.; Strobel, U.; Siegmund, W.; Rosskopf, D.; Greinacher, A.; Terasaki, T.; Kroemer, H. K. Human Platelets Express Organic Anion-Transporting Peptide 2B1, an Uptake Transporter for Atorvastatin. *Drug Metab. Dispos.* **2009**, *37*, 1129–1137.

(117) Tamai, I.; Nezu, J.; Uchino, H.; Sai, Y.; Oku, A.; Shimane, M.; Tsuji, A. Molecular Identification and Characterization of Novel Members of the Human Organic Anion Transporter (OATP) Family. *Biochem. Biophys. Res. Commun.* **2000**, *273*, 251–260.

(118) Vaidyanathan, S.; Camenisch, G.; Schuetz, H.; Reynolds, C.; Yeh, C. M.; Bizot, M. N.; Dieterich, H. A.; Howard, D.; Dole, W. P. Pharmacokinetics of the Oral Direct Renin Inhibitor Aliskiren in Combination With Digoxin, Atorvastatin, and Ketoconazole in Healthy Subjects: the Role of P-Glycoprotein in the Disposition of Aliskiren. *J. Clin. Pharmacol.* **2008**, *48*, 1323–1338.

tatin (K_m = 0.7 μM),[71] pravastatin,[121,122] and glibenclamide (K_m = 6.24 μM).[123]

Only a few genetic variants have been identified in *SLCO2B1*, and the impact of those SNPs on drug disposition needs to be further elucidated. *In vitro* experiments suggest reduced transport activity associated with the c.1457C>T variant which appears to be the result from serine to phenylalanine amino acid change at position 486 (also referred to as *SLCO2B1**3).[112] However this variant was noted to be present in only one individual, as an outlier in a pharmacokinetic study of pravastatin.[76] No effect of the *SLCO2B1**3 variant was seen on the disposition of monetlucast, however the same study reported a significant effect of the *SLCO2B1* variant c.935A>G (p.Arg312Gln) on the disposition and efficacy of this leukotriene receptor antagonist.[124] Additional studies are needed to clarify the clinical importance of OATP2B1 and its genetic variants to substrate drug disposition.

OATP1B Transporters and PXR/CAR Interplay

The potential contribution of OATP1B transporters to the regulation of CYP enzymes and other drug transporters *via* nuclear receptors such as PXR relates to the fact that many high affinity ligands for PXR such as rifampin are known substrates of OATP1B1. Other PXR ligands including paclitaxel and mifepristone have also been shown to interact with OATP1B transporters.[125] For rifampin, considering the unbound plasma concentration of this compound of approximately 0.7−2.4 μM[126] and the EC_{50} for PXR at 0.71 μM,[50] it is likely that OATP1B1 functions in a clinically relevant fashion by altering the extent of rifampin entry into hepatocytes, and thereby increasing the amount of drug available for PXR mediated transactivation of hepatic target genes. This is in accordance with previous *in vitro* results suggesting OATP1B1 as major determinant of PXR activation by rifampin,[127,128] further supported by data obtained using the *Slco1b2* knockout mouse model, where the absence of this transporter was associated with significantly reduced rifampin levels in liver of Oatp1b2 deficient mice.[129] It should be noted that the examination of the effects of OATP1B1 polymorphisms on rifampin-mediated CYP3A4-induction, where plasma 4β-hydroxycholesterol was used as an endogenous marker of CYP3A4 activity *in vivo*, failed to show any association between OATP1B1 polymorphisms (c.521T>C or −11187G>A) and the observed inductive capacity of rifampin treatment at clinical doses of this drug (600 mg for 9−11 days).[130] The lack of an OATP1B1 effect may be due to the small number of individuals studied, or the attained hepatic level of rifampin far exceeded the concentration needed for maximal PXR activation, when rifampin is given at the clinical dose of 600 mg/day. In addition it had been suggested that OATP1B1 variants are associated with changes in cholesterol metabolism pathways.[96] It should be noted OATP1B1 polymorphisms do not appear to alter rifampin-mediated changes in bilirubin elimination.[131,74]

Interestingly, it has been suggested that individuals with OATP1B1 polymorphisms may be less susceptible to drug inhibitors of this transporter. In accordance with this hypothesis, cyclosporine has been shown to increase the AUC0-∞ of repaglinide to a lesser extent in subjects with

(119) Seki, S.; Kobayashi, M.; Itagaki, S.; Hirano, T.; Iseki, K. Contribution of Organic Anion Transporting Polypeptide OATP2B1 to Amiodarone Accumulation in Lung Epithelial Cells. *Biochim. Biophys. Acta* **2009**, *1788*, 911–917.

(120) Kitamura, S.; Maeda, K.; Wang, Y.; Sugiyama, Y. Involvement of Multiple Transporters in the Hepatobiliary Transport of Rosuvastatin. *Drug Metab. Dispos.* **2008**, *36*, 2014–2023.

(121) Kobayashi, D.; Nozawa, T.; Imai, K.; Nezu, J.; Tsuji, A.; Tamai, I. Involvement of Human Organic Anion Transporting Polypeptide OATP-B (SLC21A9) in PH-Dependent Transport Across Intestinal Apical Membrane. *J. Pharmacol. Exp. Ther.* **2003**, *306*, 703–708.

(122) Nozawa, T.; Imai, K.; Nezu, J.; Tsuji, A.; Tamai, I. Functional Characterization of PH-Sensitive Organic Anion Transporting Polypeptide OATP-B in Human. *J. Pharmacol. Exp. Ther.* **2004**, *308*, 438–445.

(123) Satoh, H.; Yamashita, F.; Tsujimoto, M.; Murakami, H.; Koyabu, N.; Ohtani, H.; Sawada, Y. Citrus Juices Inhibit the Function of Human Organic Anion-Transporting Polypeptide OATP-B. *Drug Metab. Dispos.* **2005**, *33*, 518–523.

(124) Mougey, E. B.; Feng, H.; Castro, M.; Irvin, C. G.; Lima, J. J. Absorption of Montelukast Is Transporter Mediated: a Common Variant of OATP2B1 Is Associated With Reduced Plasma Concentrations and Poor Response. *Pharmacogenet. Genomics* **2009**, *19*, 129–138.

(125) Gui, C.; Miao, Y.; Thompson, L.; Wahlgren, B.; Mock, M.; Stieger, B.; Hagenbuch, B. Effect of Pregnane X Receptor Ligands on Transport Mediated by Human OATP1B1 and OATP1B3. *Eur. J. Pharmacol.* **2008**, *584*, 57–65.

(126) *Goodman & Gilman's The Pharmacological Basis of Therapeutics*; McGraw-Hill Medical Publishing Division: 2008.

(127) Tirona, R. G.; Leake, B. F.; Wolkoff, A. W.; Kim, R. B. Human Organic Anion Transporting Polypeptide-C (SLC21A6) Is a Major Determinant of Rifampin-Mediated Pregnane X Receptor Activation. *J. Pharmacol. Exp. Ther.* **2003**, *304*, 223–228.

(128) Vavricka, S. R.; Van Montfoort, J.; Ha, H. R.; Meier, P. J.; Fattinger, K. Interactions of Rifamycin SV and Rifampicin With Organic Anion Uptake Systems of Human Liver. *Hepatology* **2002**, *36*, 164–172.

(129) Zaher, H.; zu Schwabedissen, H. E.; Tirona, R. G.; Cox, M. L.; Obert, L. A.; Agrawal, N.; Palandra, J.; Stock, J. L.; Kim, R. B.; Ware, J. A. Targeted Disruption of Murine Organic Anion-Transporting Polypeptide 1b2 (Oatp1b2/Slco1b2) Significantly Alters Disposition of Prototypical Drug Substrates Pravastatin and Rifampin. *Mol. Pharmacol.* **2008**, *74*, 320–329.

(130) Niemi, M.; Kivisto, K. T.; Diczfalusy, U.; Bodin, K.; Bertilsson, L.; Fromm, M. F.; Eichelbaum, M. Effect of SLCO1B1 Polymorphism on Induction of CYP3A4 by Rifampicin. *Pharmacogenet. Genomics* **2006**, *16*, 565–568.

(131) Zhang, W.; He, Y. J.; Gan, Z.; Fan, L.; Li, Q.; Wang, A.; Liu, Z. Q.; Deng, S.; Huang, Y. F.; Xu, L. Y.; Zhou, H. H. OATP1B1 Polymorphism Is a Major Determinant of Serum Bilirubin Level but Not Associated With Rifampicin-Mediated Bilirubin Elevation. *Clin. Exp. Pharmacol. Physiol.* **2007**, *34*, 1240–1244.

the *SLCO1B1* c.521TC genotype than in those with the c.521TT genotype.[132] Studies in mice have shown that concomitant treatment with rifampin significantly increases the AUC of atorvastatin.[133] This would suggest that rifampin can function as an inhibitor of this transporter *in vivo*. This is likely the case since rifampin does not activate the mouse PXR and is thus unable to function as a significant inducer of murine Cyp3a.[15] In humans, acute dosing of rifampin is associated with elevation of substrate drugs such as atorvastatin,[134] while chronic therapy is associated with a reduction in atorvastatin level,[135] consistent with acute inhibition of OATP1B followed by chronic induction of PXR. Cyclosporine A is a potent inhibitor of drug transporters including OATP1B1 and also known to inhibit CYP3A4. Since statins such as rosuvastatin and pravastatin, which do not undergo significant metabolism, are significantly affected by coadministration of cyclosporine *in vivo*, current findings suggest that observed clinical interactions reflect the inhibition of transporters such as OATP1B1 and are not related to inhibition of drug metabolizing enzymes such as CYP3A4.[136,137] Similarly, clarithromycin, another well documented CYP3A inhibitor, has been shown to significantly elevate pravastatin levels, again consistent with recent data which identified clarithromycin as an inhibitor of OATP1B1.[138,139] Similar effects have been shown for gemfibrozil, another known OATP1B1 inhibitor.[140−142] Ezetimibe, an efficient and specific inhibitor of intestinal cholesterol absorption, is increasingly utilized as a lipid lowering agent. Both ezetimibe and its active glucuronide-metabolite levels are significantly increased during coadministration with a single-dose rifampin.[143] It had been suggested that this is due to direct inhibition of intestinal MRP2 and MDR1 by rifampin,[143] however, since ezetimibe-glucuronide has been shown to be significantly transported by OATP1B1,[144] it remains plausible that the increase in plasma level is also due to inhibition of hepatic OATP1B1. Not surprisingly, pretreatment with rifampin results in lower ezetimibe and ezetimibe glucuronide levels;[145] this is thought to result from induction of the intestinal efflux transporters MRP2 (ABCC2) and MDR1 (ABCB1).[145] Similar results have been noted for the endothelin I receptor antagonist, atrasentan, a compound which is extensively metabolized and shown to be an OATP1B1 substrate.[146] The potential for OATP1B1 mediated drug−drug interaction is supported by findings showing increased peak plasma concentrations likely due to direct inhibition of the transporter and reduced half-life due to induction of drug metabolism *via* activation of PXR after multiple doses of rifampin.[147] Elimination of bosentan, a dual endothelin receptor antagonist, has been thought to depend mostly on metabolism by CYP3A4 and CYP2C9. Remarkably, ketoconazole, one of the most potent CYP3A4

(132) Kajosaari, L. I.; Niemi, M.; Neuvonen, M.; Laitila, J.; Neuvonen, P. J.; Backman, J. T. Cyclosporine Markedly Raises the Plasma Concentrations of Repaglinide. *Clin. Pharmacol. Ther.* **2005**, *78*, 388–399.

(133) Lau, Y. Y.; Okochi, H.; Huang, Y.; Benet, L. Z. Pharmacokinetics of Atorvastatin and Its Hydroxy Metabolites in Rats and the Effects of Concomitant Rifampicin Single Doses: Relevance of First-Pass Effect From Hepatic Uptake Transporters, and Intestinal and Hepatic Metabolism. *Drug Metab. Dispos.* **2006**, *34*, 1175–1181.

(134) Lau, Y. Y.; Huang, Y.; Frassetto, L.; Benet, L. Z. Effect of OATP1B Transporter Inhibition on the Pharmacokinetics of Atorvastatin in Healthy Volunteers. *Clin. Pharmacol. Ther.* **2007**, *81*, 194–204.

(135) Backman, J. T.; Luurila, H.; Neuvonen, M.; Neuvonen, P. J. Rifampin Markedly Decreases and Gemfibrozil Increases the Plasma Concentrations of Atorvastatin and Its Metabolites. *Clin. Pharmacol. Ther.* **2005**, *78*, 154–167.

(136) Simonson, S. G.; Raza, A.; Martin, P. D.; Mitchell, P. D.; Jarcho, J. A.; Brown, C. D.; Windass, A. S.; Schneck, D. W. Rosuvastatin Pharmacokinetics in Heart Transplant Recipients Administered an Antirejection Regimen Including Cyclosporine. *Clin. Pharmacol. Ther.* **2004**, *76*, 167–177.

(137) Park, J. W.; Siekmeier, R.; Merz, M.; Krell, B.; Harder, S.; Marz, W.; Seidel, D.; Schuler, S.; Gross, W. Pharmacokinetics of Pravastatin in Heart-Transplant Patients Taking Cyclosporin A. *Int. J. Clin. Pharmacol. Ther.* **2002**, *40*, 439–450.

(138) Jacobson, T. A. Comparative Pharmacokinetic Interaction Profiles of Pravastatin, Simvastatin, and Atorvastatin When Coadministered With Cytochrome P450 Inhibitors. *Am. J. Cardiol.* **2004**, *94*, 1140–1146.

(139) Seithel, A.; Eberl, S.; Singer, K.; Auge, D.; Heinkele, G.; Wolf, N. B.; Dorje, F.; Fromm, M. F.; Konig, J. The Influence of Macrolide Antibiotics on the Uptake of Organic Anions and Drugs Mediated by OATP1B1 and OATP1B3. *Drug Metab. Dispos.* **2007**, *35*, 779–786.

(140) Kyrklund, C.; Backman, J. T.; Neuvonen, M.; Neuvonen, P. J. Gemfibrozil Increases Plasma Pravastatin Concentrations and Reduces Pravastatin Renal Clearance. *Clin. Pharmacol. Ther.* **2003**, *73*, 538–544.

(141) Nakagomi-Hagihara, R.; Nakai, D.; Tokui, T.; Abe, T.; Ikeda, T. Gemfibrozil and Its Glucuronide Inhibit the Hepatic Uptake of Pravastatin Mediated by OATP1B1. *Xenobiotica* **2007**, *37*, 474–486.

(142) Gustavson, L. E.; Schweitzer, S. M.; Koehne-Voss, S.; Achari, R.; Chira, T. O.; Esslinger, H. U.; Yannicelli, H. D. The Effects of Multiple Doses of Fenofibrate on the Pharmacokinetics of Pravastatin and Its 3alpha-Hydroxy Isomeric Metabolite. *J. Clin. Pharmacol.* **2005**, *45*, 947–953.

(143) Oswald, S.; Giessmann, T.; Luetjohann, D.; Wegner, D.; Rosskopf, D.; Weitschies, W.; Siegmund, W. Disposition and Sterol-Lowering Effect of Ezetimibe Are Influenced by Single-Dose Coadministration of Rifampin, an Inhibitor of Multidrug Transport Proteins. *Clin. Pharmacol. Ther.* **2006**, *80*, 477–485.

(144) Oswald, S.; Konig, J.; Lutjohann, D.; Giessmann, T.; Kroemer, H. K.; Rimmbach, C.; Rosskopf, D.; Fromm, M. F.; Siegmund, W. Disposition of Ezetimibe Is Influenced by Polymorphisms of the Hepatic Uptake Carrier OATP1B1. *Pharmacogenet. Genomics* **2008**, *18*, 559–568.

(145) Oswald, S.; Haenisch, S.; Fricke, C.; Sudhop, T.; Remmler, C.; Giessmann, T.; Jedlitschky, G.; Adam, U.; Dazert, E.; Warzok, R.; Wacke, W.; Cascorbi, I.; Kroemer, H. K.; Weitschies, W.; von Bergmann, K.; Siegmund, W. Intestinal Expression of P-Glycoprotein (ABCB1), Multidrug Resistance Associated Protein 2 (ABCC2), and Uridine Diphosphate-Glucuronosyltransferase 1A1 Predicts the Disposition and Modulates the Effects of the Cholesterol Absorption Inhibitor Ezetimibe in Humans. *Clin. Pharmacol. Ther.* **2006**, *79*, 206–217.

inhibitors (K_i, 0.015 μM),[148] led to a modest 2-fold increase in bosentan levels,[149] whereas rifampin, a relatively weak CYP3A4 inhibitor (K_i, 18.5 μM),[150] was capable of increasing mean bosentan plasma levels by 6.5-fold. This is consistent with available data, which suggest that bosentan is a substrate of OATP1B transporters,[151] and supported by findings in rat showing that cyclosporine A significantly inhibits hepatic accumulation of bosentan.[151,152] Repaglinide is another OATP1B1 substrate that is extensively metabolized by CYP3A4 and that has been studied for its drug interaction potential with rifampin. Pretreatment with rifampin reduced the median area under the concentration−time curve of repaglinide by about 50% compared to the untreated baseline.[153] Interestingly Bidsturp et al. showed that rifampin reduced the exposure to repaglinide by about 50%, when repaglinide was simultaneously administered with rifampin, whereas the reduction was 80% when repaglinide was administered 24 h following the last dose of rifampin.[154] This would suggest the possibility that acutely, rifampin may have an inhibitory effect, possibly on OATP1B1, whereas the inductive effects on CYP3A4 expression predominate when the circulating level of rifampin does not fully inhibit OATP but is sufficient to maintain PXR-mediated CYP3A4 induction.

(146) Katz, D. A.; Carr, R.; Grimm, D. R.; Xiong, H.; Holley-Shanks, R.; Mueller, T.; Leake, B.; Wang, Q.; Han, L.; Wang, P. G.; Edeki, T.; Sahelijo, L.; Doan, T.; Allen, A.; Spear, B. B.; Kim, R. B. Organic Anion Transporting Polypeptide 1B1 Activity Classified by SLCO1B1 Genotype Influences Atrasentan Pharmacokinetics. *Clin. Pharmacol. Ther.* **2006**, *79*, 186–196.

(147) Xiong, H.; Carr, R. A.; Locke, C. S.; Katz, D. A.; Achari, R.; Doan, T. T.; Wang, P.; Jankowski, J. R.; Sleep, D. J. Dual Effects of Rifampin on the Pharmacokinetics of Atrasentan. *J. Clin. Pharmacol.* **2007**, *47*, 423–429.

(148) Gibbs, M. A.; Thummel, K. E.; Shen, D. D.; Kunze, K. L. Inhibition of Cytochrome P-450 3A (CYP3A) in Human Intestinal and Liver Microsomes: Comparison of Ki Values and Impact of CYP3A5 Expression. *Drug Metab. Dispos.* **1999**, *27*, 180–187.

(149) van Giersbergen, P. L.; Treiber, A.; Schneiter, R.; Dietrich, H.; Dingemanse, J. Inhibitory and Inductive Effects of Rifampin on the Pharmacokinetics of Bosentan in Healthy Subjects. *Clin. Pharmacol. Ther.* **2007**, *81*, 414–419.

(150) Kajosaari, L. I.; Laitila, J.; Neuvonen, P. J.; Backman, J. T. Metabolism of Repaglinide by CYP2C8 and CYP3A4 in Vitro: Effect of Fibrates and Rifampicin. *Basic Clin. Pharmacol. Toxicol.* **2005**, *97*, 249–256.

(151) Treiber, A.; Schneiter, R.; Hausler, S.; Stieger, B. Bosentan Is a Substrate of Human OATP1B1 and OATP1B3: Inhibition of Hepatic Uptake As the Common Mechanism of Its Interactions With Cyclosporin A, Rifampicin, and Sildenafil. *Drug Metab. Dispos.* **2007**, *35*, 1400–1407.

(152) Treiber, A.; Schneiter, R.; Delahaye, S.; Clozel, M. Inhibition of Organic Anion Transporting Polypeptide-Mediated Hepatic Uptake Is the Major Determinant in the Pharmacokinetic Interaction Between Bosentan and Cyclosporin A in the Rat. *J. Pharmacol. Exp. Ther.* **2004**, *308*, 1121–1129.

(153) Niemi, M.; Backman, J. T.; Neuvonen, M.; Neuvonen, P. J.; Kivisto, K. T. Rifampin Decreases the Plasma Concentrations and Effects of Repaglinide. *Clin. Pharmacol. Ther.* **2000**, *68*, 495–500.

(154) Bidstrup, T. B.; Stilling, N.; Damkier, P.; Scharling, B.; Thomsen, M. S.; Brosen, K. Rifampicin Seems to Act As Both an Inducer and an Inhibitor of the Metabolism of Repaglinide. *Eur. J. Clin. Pharmacol.* **2004**, *60*, 109–114.

(155) Chen, Y.; Kissling, G.; Negishi, M.; Goldstein, J. A. The Nuclear Receptors Constitutive Androstane Receptor and Pregnane X Receptor Cross-Talk With Hepatic Nuclear Factor 4alpha to Synergistically Activate the Human CYP2C9 Promoter. *J. Pharmacol. Exp. Ther.* **2005**, *314*, 1125–1133.

(156) Ferguson, S. S.; LeCluyse, E. L.; Negishi, M.; Goldstein, J. A. Regulation of Human CYP2C9 by the Constitutive Androstane Receptor: Discovery of a New Distal Binding Site. *Mol. Pharmacol.* **2002**, *62*, 737–746.

(157) Chen, Y.; Ferguson, S. S.; Negishi, M.; Goldstein, J. A. Induction of Human CYP2C9 by Rifampicin, Hyperforin, and Phenobarbital Is Mediated by the Pregnane X Receptor. *J. Pharmacol. Exp. Ther.* **2004**, *308*, 495–501.

(158) Chen, Y.; Ferguson, S. S.; Negishi, M.; Goldstein, J. A. Identification of Constitutive Androstane Receptor and Glucocorticoid Receptor Binding Sites in the CYP2C19 Promoter. *Mol. Pharmacol.* **2003**, *64*, 316–324.

(159) Wang, H.; Faucette, S.; Sueyoshi, T.; Moore, R.; Ferguson, S.; Negishi, M.; LeCluyse, E. L. A Novel Distal Enhancer Module Regulated by Pregnane X Receptor/Constitutive Androstane Receptor Is Essential for the Maximal Induction of CYP2B6 Gene Expression. *J. Biol. Chem.* **2003**, *278*, 14146–14152.

(160) Wang, H.; Faucette, S.; Moore, R.; Sueyoshi, T.; Negishi, M.; LeCluyse, E. Human Constitutive Androstane Receptor Mediates Induction of CYP2B6 Gene Expression by Phenytoin. *J. Biol. Chem.* **2004**, *279*, 29295–29301.

(161) Goodwin, B.; Moore, L. B.; Stoltz, C. M.; McKee, D. D.; Kliewer, S. A. Regulation of the Human CYP2B6 Gene by the Nuclear Pregnane X Receptor. *Mol. Pharmacol.* **2001**, *60*, 427–431.

(162) Sugatani, J.; Nishitani, S.; Yamakawa, K.; Yoshinari, K.; Sueyoshi, T.; Negishi, M.; Miwa, M. Transcriptional Regulation of Human UGT1A1 Gene Expression: Activated Glucocorticoid Receptor Enhances Constitutive Androstane Receptor/Pregnane X Receptor-Mediated UDP-Glucuronosyltransferase 1A1 Regulation With Glucocorticoid Receptor-Interacting Protein 1. *Mol. Pharmacol.* **2005**, *67*, 845–855.

(163) Sugatani, J.; Mizushima, K.; Osabe, M.; Yamakawa, K.; Kakizaki, S.; Takagi, H.; Mori, M.; Ikari, A.; Miwa, M. Transcriptional Regulation of Human UGT1A1 Gene Expression Through Distal and Proximal Promoter Motifs: Implication of Defects in the UGT1A1 Gene Promoter. *Naunyn Schmiedebergs Arch. Pharmacol.* **2008**, *377*, 597–605.

(164) Gardner-Stephen, D.; Heydel, J. M.; Goyal, A.; Lu, Y.; Xie, W.; Lindblom, T.; Mackenzie, P.; Radominska-Pandya, A. Human PXR Variants and Their Differential Effects on the Regulation of Human UDP-Glucuronosyltransferase Gene Expression. *Drug Metab. Dispos.* **2004**, *32*, 340–347.

(165) Echchgadda, I.; Song, C. S.; Oh, T.; Ahmed, M.; De, L. C.; IChatterjee, B. The Xenobiotic-Sensing Nuclear Receptors Pregnane X Receptor, Constitutive Androstane Receptor, and Orphan Nuclear Receptor Hepatocyte Nuclear Factor 4alpha in the Regulation of Human Steroid-/Bile Acid-Sulfotransferase. *Mol. Endocrinol.* **2007**, *21*, 2099–2111.

Conclusion

There is an increasing appreciation of the role of drug transporter to the drug disposition process. Importantly, it is now becoming clear that coordinated expression and function of metabolizing enzymes, and nuclear receptors are needed to ensure organs such as the liver efficiently remove endogenous and xenobiotic compounds from the systemic circulation. Hepatic drug uptake transporters such as OATP1B1 and OATP1B3 represent the first step that determines the

(166) Arnold, K. A.; Eichelbaum, M.; Burk, O. Alternative Splicing Affects the Function and Tissue-Specific Expression of the Human Constitutive Androstane Receptor. *Nucl. Recept.* **2004**, *2*, 1.

(167) Burk, O.; Arnold, K. A.; Nussler, A. K.; Schaeffeler, E.; Efimova, E.; Avery, B. A.; Avery, M. A.; Fromm, M. F.; Eichelbaum, M. Antimalarial Artemisinin Drugs Induce Cytochrome P450 and MDR1 Expression by Activation of Xenosensors Pregnane X Receptor and Constitutive Androstane Receptor. *Mol. Pharmacol.* **2005**, *67*, 1954–1965.

(168) Geick, A.; Eichelbaum, M.; Burk, O. Nuclear Receptor Response Elements Mediate Induction of Intestinal MDR1 by Rifampin. *J. Biol. Chem.* **2001**, *276*, 14581–14587.

(169) Assem, M.; Schuetz, E. G.; Leggas, M.; Sun, D.; Yasuda, K.; Reid, G.; Zelcer, N.; Adachi, M.; Strom, S.; Evans, R. M.; Moore, D. D.; Borst, P.; Schuetz, J. D. Interactions Between Hepatic Mrp4 and Sult2a As Revealed by the Constitutive Androstane Receptor and Mrp4 Knockout Mice. *J. Biol. Chem.* **2004**, *279*, 22250–22257.

(170) Meyer zu Schwabedissen, H. E.; Tirona, R. G.; Yip, C. S.; Ho, R. H.; Kim, R. B. Interplay Between the Nuclear Receptor Pregnane X Receptor and the Uptake Transporter Organic Anion Transporter Polypeptide 1A2 Selectively Enhances Estrogen Effects in Breast Cancer. *Cancer Res.* **2008**, *68*, 9338–9347.

(171) Miki, Y.; Suzuki, T.; Kitada, K.; Yabuki, N.; Shibuya, R.; Moriya, T.; Ishida, T.; Ohuchi, N.; Blumberg, B.; Sasano, H. Expression of the Steroid and Xenobiotic Receptor and Its Possible Target Gene, Organic Anion Transporting Polypeptide-A, in Human Breast Carcinoma. *Cancer Res.* **2006**, *66*, 535–542.

(172) Cui, Y.; Konig, J.; Leier, I.; Buchholz, U.; Keppler, D. Hepatic Uptake of Bilirubin and Its Conjugates by the Human Organic Anion Transporter SLC21A6. *J. Biol. Chem.* **2001**, *276*, 9626–9630.

(173) Briz, O.; Romero, M. R.; Martinez-Becerra, P.; MacIas, R. I.; Perez, M. J.; Jimenez, F.; San Martin, F. G.; Marin, J. J. OATP8/1B3-Mediated Cotransport of Bile Acids and Glutathione: an Export Pathway for Organic Anions From Hepatocytes? *J. Biol. Chem.* **2006**, *281*, 30326–30335.

(174) Maeda, K.; Kambara, M.; Tian, Y.; Hofmann, A. F.; Sugiyama, Y. Uptake of Ursodeoxycholate and Its Conjugates by Human Hepatocytes: Role of Na(+)-Taurocholate Cotransporting Polypeptide (NTCP), Organic Anion Transporting Polypeptide (OATP) 1B1 (OATP-C), and Oatp1B3 (OATP8). *Mol. Pharmaceutics* **2006**, *3*, 70–77.

(175) Yamaguchi, H.; Kobayashi, M.; Okada, M.; Takeuchi, T.; Unno, M.; Abe, T.; Goto, J.; Hishinuma, T.; Mano, N. Rapid Screening of Antineoplastic Candidates for the Human Organic Anion Transporter OATP1B3 Substrates Using Fluorescent Probes. *Cancer Lett.* **2008**, *260*, 163–169.

(176) Yamaguchi, H.; Okada, M.; Akitaya, S.; Ohara, H.; Mikkaichi, T.; Ishikawa, H.; Sato, M.; Matsuura, M.; Saga, T.; Unno, M.; Abe, T.; Mano, N.; Hishinuma, T.; Goto, J. Transport of Fluorescent Chenodeoxycholic Acid Via the Human Organic Anion Transporters OATP1B1 and OATP1B3. *J. Lipid Res.* **2006**, *47*, 1196–1202.

(177) Nakai, D.; Nakagomi, R.; Furuta, Y.; Tokui, T.; Abe, T.; Ikeda, T.; Nishimura, K. Human Liver-Specific Organic Anion Transporter, LST-1, Mediates Uptake of Pravastatin by Human Hepatocytes. *J. Pharmacol. Exp. Ther.* **2001**, *297*, 861–867.

(178) Konig, J.; Cui, Y.; Nies, A. T.; Keppler, D. Localization and Genomic Organization of a New Hepatocellular Organic Anion Transporting Polypeptide. *J. Biol. Chem.* **2000**, *275*, 23161–23168.

(179) Hirano, M.; Maeda, K.; Shitara, Y.; Sugiyama, Y. Contribution of OATP2 (OATP1B1) and OATP8 (OATP1B3) to the Hepatic Uptake of Pitavastatin in Humans. *J. Pharmacol. Exp. Ther.* **2004**, *311*, 139–146.

(180) Takada, T.; Weiss, H. M.; Kretz, O.; Gross, G.; Sugiyama, Y. Hepatic Transport of PKI166, an Epidermal Growth Factor Receptor Kinase Inhibitor of the Pyrrolo-Pyrimidine Class, and Its Main Metabolite, ACU154. *Drug Metab. Dispos.* **2004**, *32*, 1272–1278.

(181) Letschert, K.; Faulstich, H.; Keller, D.; Keppler, D. Molecular Characterization and Inhibition of Amanitin Uptake into Human Hepatocytes. *Toxicol. Sci.* **2006**, *91*, 140–149.

(182) Lu, W. J.; Tamai, I.; Nezu, J.; Lai, M. L.; Huang, J. D. Organic Anion Transporting Polypeptide-C Mediates Arsenic Uptake in HEK-293Cells. *J. Biomed. Sci.* **2006**, *13*, 525–533.

(183) Lau, Y. Y.; Okochi, H.; Huang, Y.; Benet, L. Z. Multiple Transporters Affect the Disposition of Atorvastatin and Its Two Active Hydroxy Metabolites: Application of in Vitro and Ex Situ Systems. *J. Pharmacol. Exp. Ther.* **2006**, *316*, 762–771.

(184) Briz, O.; Serrano, M. A.; Rebollo, N.; Hagenbuch, B.; Meier, P. J.; Koepsell, H.; Marin, J. J. Carriers Involved in Targeting the Cytostatic Bile Acid-Cisplatin Derivatives Cis-Diammine-Chloro-Cholylglycinate-Platinum(II) and Cis-Diammine-Bisursodeoxycholate-Platinum(II) Toward Liver Cells. *Mol. Pharmacol.* **2002**, *61*, 853–860.

(185) Sandhu, P.; Lee, W.; Xu, X.; Leake, B. F.; Yamazaki, M.; Stone, J. A.; Lin, J. H.; Pearson, P. G.; Kim, R. B. Hepatic Uptake of the Novel Antifungal Agent Caspofungin. *Drug Metab. Dispos.* **2005**, *33*, 676–682.

(186) Shitara, Y.; Hirano, M.; Sato, H.; Sugiyama, Y. Gemfibrozil and Its Glucuronide Inhibit the Organic Anion Transporting Polypeptide 2 (OATP2/OATP1B1:SLC21A6)-Mediated Hepatic Uptake and CYP2C8-Mediated Metabolism of Cerivastatin: Analysis of the Mechanism of the Clinically Relevant Drug-Drug Interaction Between Cerivastatin and Gemfibrozil. *J. Pharmacol. Exp. Ther.* **2004**, *311*, 228–236.

(187) Meier-Abt, F.; Faulstich, H.; Hagenbuch, B. Identification of Phalloidin Uptake Systems of Rat and Human Liver. *Biochim. Biophys. Acta* **2004**, *1664*, 64–69.

(188) Liu, L.; Cui, Y.; Chung, A. Y.; Shitara, Y.; Sugiyama, Y.; Keppler, D.; Pang, K. S. Vectorial Transport of Enalapril by Oatp1a1/Mrp2 and OATP1B1 and OATP1B3/MRP2 in Rat and Human Livers. *J. Pharmacol. Exp. Ther.* **2006**, *318*, 395–402.

(189) Shimizu, M.; Fuse, K.; Okudaira, K.; Nishigaki, R.; Maeda, K.; Kusuhara, H.; Sugiyama, Y. Contribution of OATP (Organic Anion-Transporting Polypeptide) Family Transporters to the Hepatic Uptake of Fexofenadine in Humans. *Drug Metab. Dispos.* **2005**, *33*, 1477–1481.

(190) Baldes, C.; Koenig, P.; Neumann, D.; Lenhof, H. P.; Kohlbacher, O.; Lehr, C. M. Development of a Fluorescence-Based Assay for Screening of Modulators of Human Organic Anion Transporter 1B3 (OATP1B3). *Eur. J. Pharm. Biopharm.* **2006**, *62*, 39–43.

extent of hepatic drug entry and the potential to activate xenosensor nuclear receptors such as PXR and CAR. Therefore the apparent intersubject variability in drug metabolism may be not only reflective of genetic variation in phase I and phase II enzyme but also linked to genetic variation in drug uptake transporters such as OATP1B1 that can modulate the hepatocellular concentration of ligands for nuclear receptors such as PXR and CAR. Accordingly, in order to better predict drug drug transporters, disposition and drug−drug interactions in humans, it will be essential that drug uptake transporters such as OATP1B1 and OATP1B3 are included as potential determinants of variation in drug responsiveness.

Acknowledgment. This work was supported in part by a CIHR grant (MOP-89753) and a Deutsche Forschungsgemeinschafts (ME 3090/1-1) grant.

MP9000298

(191) Fischer, W. J.; Altheimer, S.; Cattori, V.; Meier, P. J.; Dietrich, D. R.; Hagenbuch, B. Organic Anion Transporting Polypeptides Expressed in Liver and Brain Mediate Uptake of Microcystin. *Toxicol. Appl. Pharmacol.* **2005**, *203*, 257–263.

(192) Komatsu, M.; Furukawa, T.; Ikeda, R.; Takumi, S.; Nong, Q.; Aoyama, K.; Akiyama, S.; Keppler, D.; Takeuchi, T. Involvement of Mitogen-Activated Protein Kinase Signaling Pathways in Microcystin-LR-Induced Apoptosis After Its Selective Uptake Mediated by OATP1B1 and OATP1B3. *Toxicol. Sci.* **2007**, *97*, 407–416.

(193) Nakagomi-Hagihara, R.; Nakai, D.; Kawai, K.; Yoshigae, Y.; Tokui, T.; Abe, T.; Ikeda, T. OATP1B1, OATP1B3, and Mrp2 Are Involved in Hepatobiliary Transport of Olmesartan, a Novel Angiotensin II Blocker. *Drug Metab. Dispos.* **2006**, *34*, 862–869.

(194) Yamada, A.; Maeda, K.; Kamiyama, E.; Sugiyama, D.; Kondo, T.; Shiroyanagi, Y.; Nakazawa, H.; Okano, T.; Adachi, M.; Schuetz, J. D.; Adachi, Y.; Hu, Z.; Kusuhara, H.; Sugiyama, Y. Multiple Human Isoforms of Drug Transporters Contribute to the Hepatic and Renal Transport of Olmesartan, a Selective Antagonist of the Angiotensin II AT1-Receptor. *Drug Metab. Dispos.* **2007**, *35*, 2166–2176.

(195) Fehrenbach, T.; Cui, Y.; Faulstich, H.; Keppler, D. Characterization of the Transport of the Bicyclic Peptide Phalloidin by Human Hepatic Transport Proteins. *Naunyn Schmiedebergs Arch. Pharmacol.* **2003**, *368*, 415–420.

(196) Fujino, H.; Nakai, D.; Nakagomi, R.; Saito, M.; Tokui, T.; Kojima, J. Metabolic Stability and Uptake by Human Hepatocytes of Pitavastatin, a New Inhibitor of HMG-CoA Reductase. *Arzneimittelforschung* **2004**, *54*, 382–388.

(197) Sasaki, M.; Suzuki, H.; Ito, K.; Abe, T.; Sugiyama, Y. Transcellular Transport of Organic Anions Across a Double-Transfected Madin-Darby Canine Kidney II Cell Monolayer Expressing Both Human Organic Anion-Transporting Polypeptide (OATP2/SLC21A6) and Multidrug Resistance-Associated Protein 2 (MRP2/ABCC2). *J. Biol. Chem.* **2002**, *277*, 6497–6503.

(198) Schneck, D. W.; Birmingham, B. K.; Zalikowski, J. A.; Mitchell, P. D.; Wang, Y.; Martin, P. D.; Lasseter, K. C.; Brown, C. D.; Windass, A. S.; Raza, A. The Effect of Gemfibrozil on the Pharmacokinetics of Rosuvastatin. *Clin. Pharmacol. Ther.* **2004**, *75*, 455–463.

(199) Sakamoto, S.; Kusuhara, H.; Horie, K.; Takahashi, K.; Baba, T.; Ishizaki, J.; Sugiyama, Y. Identification of the Transporters Involved in the Hepatobiliary Transport and Intestinal Efflux of Methyl 1-(3,4-Dimethoxyphenyl)-3-(3-Ethylvaleryl)-4-Hydroxy-6,7,8-Trimethoxy-2-Naphthoate (S-8921) Glucuronide, a Pharmacologically Active Metabolite of S-8921. *Drug Metab. Dispos.* **2008**, *36*, 1553–1561.

(200) Sakamoto, K.; Mikami, H.; Kimura, J. Involvement of Organic Anion Transporting Polypeptides in the Toxicity of Hydrophilic Pravastatin and Lipophilic Fluvastatin in Rat Skeletal Myofibres. *Br. J. Pharmacol.* **2008**, *154*, 1482–1490.

(201) Tsuda-Tsukimoto, M.; Maeda, T.; Iwanaga, T.; Kume, T.; Tamai, I. Characterization of Hepatobiliary Transport Systems of a Novel Alpha4beta1/Alpha4beta7 Dual Antagonist, TR-14035. *Pharm. Res.* **2006**, *23*, 2646–2656.

(202) Nozawa, T.; Sugiura, S.; Nakajima, M.; Goto, A.; Yokoi, T.; Nezu, J.; Tsuji, A.; Tamai, I. Involvement of Organic Anion Transporting Polypeptides in the Transport of Troglitazone Sulfate: Implications for Understanding Troglitazone Hepatotoxicity. *Drug Metab. Dispos.* **2004**, *32*, 291–294.

(203) Yamashiro, W.; Maeda, K.; Hirouchi, M.; Adachi, Y.; Hu, Z.; Sugiyama, Y. Involvement of Transporters in the Hepatic Uptake and Biliary Excretion of Valsartan, a Selective Antagonist of the Angiotensin II AT1-Receptor, in Humans. *Drug Metab. Dispos.* **2006**, *34*, 1247–1254.