

MINIREVIEW

Organic Anion Transporting Polypeptides: Emerging Roles in Cancer Pharmacology

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ABSTRACT

The organic anion transporting polypeptides (OATPs) are a superfamily of drug transporters involved in the uptake and disposition of a wide array of structurally divergent endogenous and exogenous substrates, including steroid hormones, bile acids, and commonly used drugs, such as anti-infectives, antihypertensives, and cholesterol lowering agents. In the past decade, OATPs, primarily OATP1A2, OATP1B1, and OATP1B3, have emerged as potential mediators of chemotherapy disposition, including drugs such as methotrexate, doxorubicin, paclitaxel, docetaxel, irinotecan and its important metabolite 7-ethyl-10-hydroxycamptothecin, and certain tyrosine kinase inhibitors. Furthermore, OATP family members are polymorphic and numerous studies have shown OATP variants to have

differential uptake, disposition, and/or pharmacokinetics of numerous drug substrates with important implications for interindividual differences in efficacy and toxicity. Additionally, certain OATPs have been found to be overexpressed in a variety of human solid tumors, including breast, liver, colon, pancreatic, and ovarian cancers, suggesting potential roles for OATPs in tumor development and progression and as novel targets for cancer therapy. This review focuses on the emerging roles for selected OATPs in cancer pharmacology, including preclinical and clinical studies suggesting roles in chemotherapy disposition, the pharmacogenetics of OATPs in cancer therapy, and OATP overexpression in various tumor tissues with implications for OATPs as therapeutic targets.

Introduction

The solute carrier superfamily encompasses many transporters that play important roles in the uptake and distribution of both endogenous compounds and xenobiotics (Hagenbuch and Stieger, 2013). Among these are the organic anion transporting polypeptides (OATPs), classified in the *SLCO* family, which transport a large number of structurally diverse amphipathic substrates including steroid hormones (which are important for proliferation of hormone-dependent cancers) (De Bruyn et al., 2011), bile acids, statins, antihypertensives, antibiotics, antifungals, and chemotherapeutic agents (Hagenbuch and Stieger, 2013). Since the discovery of the first OATP in 1994 (Jacquemin et al., 1994), over 300 OATP family members

have been identified in over 40 species, including 11 human transporters and many transporters in rats and mice (Hagenbuch and Stieger, 2013).

While many human OATPs have direct rodent orthologs, this is not necessarily the case for OATP1A2, OATP1B1, and OATP1B3, in which the rodent transporters have high sequence homology to the human transporters but are not direct orthologs. There are four known members of the *Oatp1a* family in mice (*Oatp1a1*, *Oatp1a4*, *Oatp1a5*, and *Oatp1a6*), in contrast to one human member (OATP1A2), but only one mouse *Oatp1b* transporter (*Oatp1b2*) compared with two human transporters (OATP1B1 and OATP1B3). Based on localization patterns of these transporters, it is thought that murine *Oatp1b2* is the closest ortholog to human OATP1B1 and OATP1B3, but *Oatp1a1* and *Oatp1a4* may also fulfill similar functions. For OATP1A2, the closest murine isoform *Oatp1a4* exhibits 72% amino acid sequence homology; however, additional isoforms *Oatp1a1*, *Oatp1a5*, and *Oatp1a6* may also have similar roles based on tissue localization. While *Oatp1b2* null mice are often used to mimic the loss of

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ABBREVIATIONS: ABC, ATP-binding cassette; AUC, area under the plasma time-concentration curve; Bamef-R2, cis-diamminechlorocholylglycinate-platinum(II); Bamef-UD2, cis-diammine-bisursodeoxycholate-platinum(II); DHEAS, dehydroepiandrosterone sulfate; E3S, estrone-3-sulfate; HEK, human embryonic kidney; OATP, organic anion transporting polypeptide; OCT, organic cation transporter; P450, cytochrome P450; rs, reference single nucleotide polymorphism; SN-38, 7-ethyl-10-hydroxycamptothecin; SNP, single nucleotide polymorphism; TKI, tyrosine kinase inhibitor.

OATP1B1 and OATP1B3 function, this is potentially problematic because the *Oatp1a* transporters may be able to partially recover substrate transport when *Oatp1b2* is absent. For this reason, the utilization of *Oatp1a/Oatp1b* null mice to prevent compensation from *Oatp1a* transporters when studying the impact of the loss of *Oatp1b* function on substrate transport may be a significant factor to consider (Iusuf et al., 2012). Additionally, several humanized mouse strains have been created using *Oatp1a/Oatp1b* null mice with expression of human OATP1A2, OATP1B1, or OATP1B3 in the liver parenchymal cells. These humanized mice have allowed for better study of the effect of each human transporter individually. The limitations for the use of these mouse models were summarized in a recent review and should be considered when interpreting data from mouse model studies given the lack of direct rodent orthologs for important OATP transporters (Durmus et al., 2016). To date, no mouse model has been published for OATP2B1.

The genes encoding several human OATPs (in particular, *SLCO1B1*, *SLCO1B3*, and *SLCO1A2*) are located on chromosome 12, while genes for other OATPs are spread throughout the rest of the genome. All members of the OATP family contain 12 putative transmembrane domains with conserved cysteine residues in an extracellular loop between transmembrane domains 9 and 10, as well as signature sequences containing *N*-glycosylation sites in other extracellular loops (Hagenbuch and Meier, 2004; König, 2011). The OATPs are organized into families (in which members have at least 40% sequence homology; denoted by a number) and subfamilies (in which members have at least 60% sequence homology; denoted by a letter), with individual members of each subfamily identified numerically. The OATP designation is used for human transporters, while *Oatp* is used for nonhuman transporters (Hagenbuch and Meier, 2004).

Because of their wide range of transported substrates, OATPs have important roles both in the kinetics of drug disposition and in drug-drug interactions when two or more xenobiotics that are a substrate for the same OATP are given concurrently (Kindla et al., 2009; Shitara, 2011; König et al., 2013). Additionally, several drugs are known to inhibit the function of one or more OATP, notably inhibition of OATP1B1 and OATP1B3 by macrolide antibiotics and rifampicin, inhibition of OATP1B1 by cyclosporine (Clarke and Cherrington, 2012; König et al., 2013), and inhibition of all OATPs by rifamycin (Hagenbuch and Meier, 2004). Intestinal OATP2B1 is inhibited by baicalin, cefixime, and fruit juices (most notably apple juice; also orange and grapefruit juices) (Dresser et al., 2002; Clarke and Cherrington, 2012; Shirasaka et al., 2013; Fujita et al., 2016), while OATP1A2 is inhibited by grapefruit juice (specifically its component naringin) (Glaeser et al., 2007; Clarke and Cherrington, 2012; Rebello et al., 2012). Testosterone and progesterone (and steroid hormones closely related to them) inhibit OATP2B1-mediated transport but are not substrates for OATP2B1 (Grube et al., 2006a). These inhibitors may be clinically useful as a therapeutic strategy to increase oral bioavailability and increase systemic exposure for drugs with high first-pass metabolism by the liver, given the important role of OATPs in taking up substrates into hepatocytes for further processing (Hagenbuch and Stieger, 2013). The International Transporter Consortium has published guidelines regarding recommended testing to determine if new drugs are inhibitors of OATPs (Giacomini et al.,

2010). Difficulty can arise when studying the effect of OATP inhibitors since some of these compounds also inhibit cytochrome P450 (P450) enzymes and other transporters (Koenen et al., 2011). Additionally, data for localization and transport of compounds by OATPs can vary based on the cell type and method of detection used, which likely contributes to some conflicting results in the literature that are summarized in this review.

Transport by OATPs is sodium independent, pH dependent, and electroneutral, and OATP substrates tend to be highly albumin bound in plasma circulation (Hagenbuch and Meier, 2004). The exact mechanism of transport by OATPs is not fully known and may vary by substrate for an individual transporter (Hagenbuch and Stieger, 2013). Closely related OATPs may have different substrate profiles, as is the case for OATP1B1 and OATP1B3, which each have unique substrates. However, they also have shared substrate transport capacity for classes of drugs such as statins, angiotensin receptor antagonists, and human immunodeficiency virus protease inhibitors. OATPs have been found in nearly every human tissue, commonly (but not always) located in the basolateral membrane of polarized cells (König, 2011). Certain OATPs, such as OATP1B1, OATP1B3, OATP1A2, and OATP2B1, are primarily expressed in tissues important to drug disposition, including liver, kidney, and intestine, and at the blood-brain barrier (Fig. 1). The regulation of OATP expression is complex, with both transcriptional and post-transcriptional components (Hagenbuch and Stieger, 2013). This review will focus on four widely studied OATPs and their roles in cancer pharmacology: OATP1A2, OATP1B1, OATP1B3, and OATP2B1. Table 1 provides an overview of each of these key OATPs including major sites of expression in normal tissues and prototypical substrates.

OATP1A2 is found predominantly in the brain at the blood-brain barrier (Gao et al., 2000; Tamai et al., 2000; Kusuhara and Sugiyama, 2005), testis (Tamai et al., 2000), renal proximal tubule cells (Kullak-Ublick et al., 1995), liver cholangiocytes but not hepatocytes (Lee et al., 2005), prostate (Tamai et al., 2000), and ciliary body epithelium (Gao et al., 2005). There are conflicting data regarding intestinal expression of OATP1A2, but it is generally not considered to be highly expressed in this tissue (Tamai et al., 2000; Glaeser et al., 2007; Hilgendorf et al., 2007; Meier et al., 2007; Tamai, 2012; Gröer et al., 2013; Drozdziak et al., 2014). OATP1B1 and OATP1B3 are found almost exclusively at the basolateral membrane of hepatocytes under normal conditions (Tamai et al., 2000; Cui et al., 2003; König, 2011; Iusuf et al., 2012). However, one study found low OATP1B3 mRNA expression in the kidney (Hilgendorf et al., 2007), and there are conflicting data indicating expression in the intestine with one study finding OATP1B1 and OATP1B3 mRNA expression in the small intestine (Glaeser et al., 2007) and another finding neither protein nor mRNA expression of these transporters along the entire intestinal tract (Drozdziak et al., 2014).

Among all hepatic transporters, OATP1B1 and OATP1B3 were found to have the highest and second highest, respectively, protein abundance in healthy Caucasian subjects (Burt et al., 2016); in another study OATP1B1 was among the most abundant transporters in terms of liver protein levels, while OATP1B3 protein levels were moderate compared with other transporters (Hilgendorf et al., 2007). OATP2B1 is ubiquitously expressed in fetal and adult tissues and notably is found at the

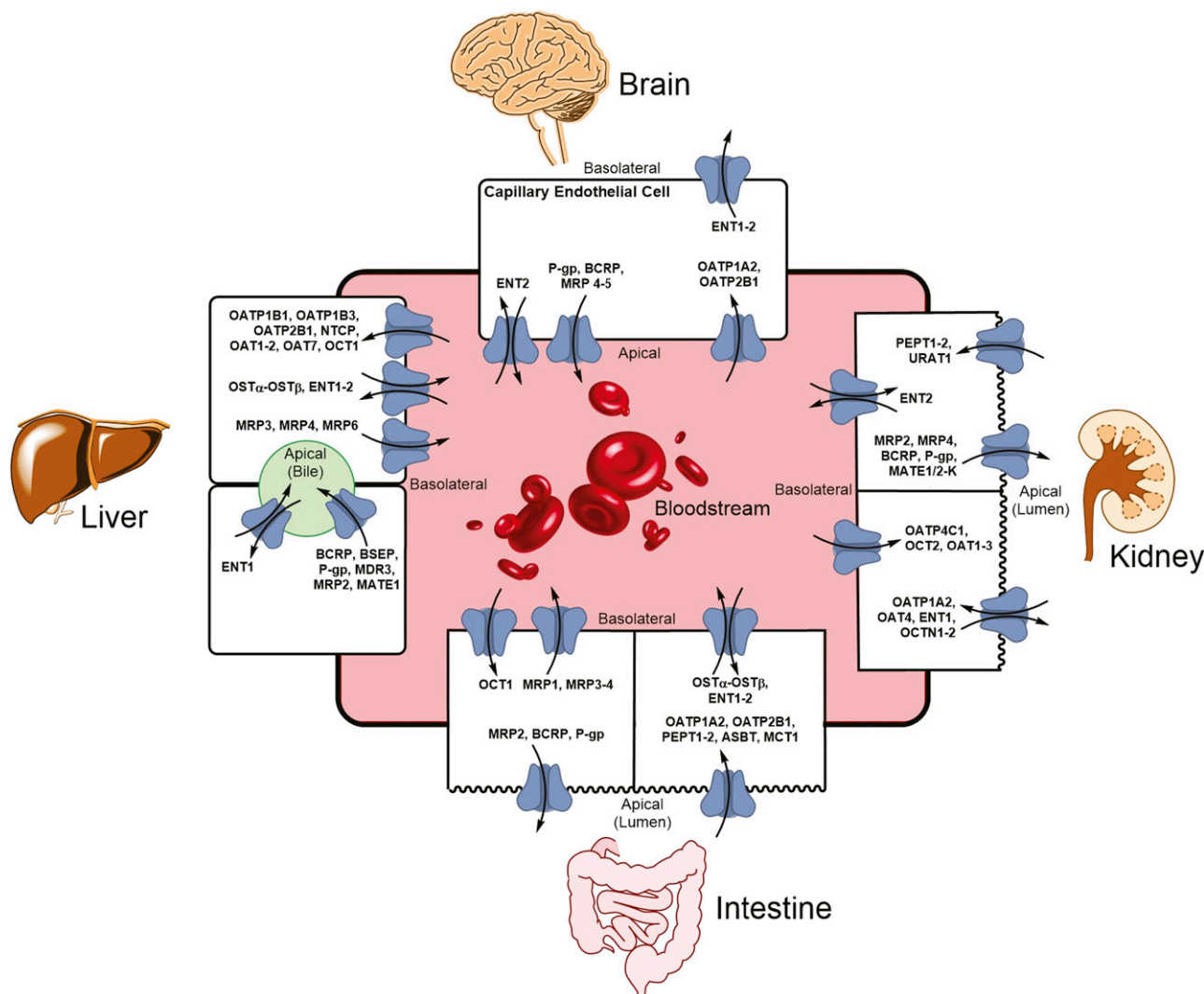


Fig. 1. Organ-specific expression of drug transporters. The expression of transporters at the apical and basolateral membranes of various tissues plays a crucial role in the transport of both endogenous and exogenous substrates across membranes. In the liver and kidney, transporters mediate movement of substrates into hepatocytes or the proximal tubule cells, respectively, where the substrates may undergo biotransformation or be excreted unmodified into the bile or urine via other transporters. In the intestine, transporters are involved in the selective movement of substrates into and out of enterocytes, which affects the oral bioavailability of drugs. In the capillary endothelial cells of the blood-brain barrier, transporters control which substrates can cross from the bloodstream into brain cells, thus limiting the ability of certain substrates to penetrate brain tissue. For the liver, the bloodstream compartment refers to the portal venous circulation. ASBT, apical sodium-dependent bile acid transporter; BCRP, breast cancer resistance protein; ENT, equilibrative nucleoside transporter; MATE, multidrug and toxic compound extrusion; MCT, monocarboxylate transporter; MRP, multidrug resistance-associated protein; NTCP, sodium/taurocholate cotransporting polypeptide; OAT, organic anion transporter; OST, organic solute and steroid transporter; PEPT, peptide transporter; P-gp, P-glycoprotein.

apical membrane of enterocytes (Kobayashi et al., 2003; Sai et al., 2006; Meier et al., 2007; Iusuf et al., 2012; Tamai, 2012), the basolateral membrane of hepatocytes (Kullak-Ublick et al., 2001), the apical membrane of renal proximal tubule cells, and the blood-brain barrier (Iusuf et al., 2012), as well as in the heart (Grube et al., 2006b), pancreas, lung, ovary, testis, spleen (Tamai et al., 2000), ciliary body epithelium (Gao et al., 2005), and placenta (St-Pierre et al., 2002).

The Role of OATP Transporters in Chemotherapy Disposition

It is widely known that OATPs represent an important family of transporters with important roles in drug uptake and distribution. A growing number of chemotherapeutic agents

have been shown to be transported by OATP1A2, OATP1B1, OATP1B3, and OATP2B1, primarily in preclinical studies utilizing *in vitro* cell-based systems or *in vivo* animal models (Thakkar et al., 2015; Durmus et al., 2016). Emerging data suggest potential roles for these OATPs in relation to the clinical pharmacology of specific chemotherapeutic agents. In addition, chemotherapy agents may affect the transport of other substances by OATPs and contribute to drug-drug interactions. There are little published data regarding chemotherapeutic agent-specific transporter-mediated drug-drug interactions. Marada et al. (2015) used human embryonic kidney (HEK) cells stably transfected with human OATP1B1 and OATP1B3 to study the interaction of 26 different chemotherapy drugs with these transporters by assessing the change in transport of prototypic substrates—estrone-3-sulfate (E3S)

TABLE 1

Overview of selected *SLCO* transporters

The table was adapted from Ho and Kim (2010) and König (2011).

Gene Symbol	Protein	Normal Tissue Distribution	Cellular Localization	Example Substrates
<i>SLCO1A2</i> (formerly <i>SLC21A3</i>)	OATP1A2 (formerly OATP-A, OATP1)	Brain (blood-brain barrier), kidney, liver, intestine, eye, placenta, prostate, testis	BL (ciliary body epithelia) AP (kidney, hepatocytes, intestine)	Chemotherapy: atrasentan, chemotherapy-bile acid conjugates (i.e., Bamet-R2, Bamet-UD2, chlorambucil taurocholate), docetaxel, imatinib, methotrexate, microcystin-LR Other: xenobiotics: BSP, deltorphin, fexofenadine, gadolinium dye for MRI, ouabain, rosuvastatin, levofloxacin, DPDPE, rocuronium, saquinavir; endogenous: bile salts, T ₄ , T ₃ , PGE ₂ , E2G, E3S, DHEAS
<i>SLCO1B1</i> (formerly <i>SLC21A6</i>)	OATP1B1 (formerly LST-1, OATP-C, OATP2)	Liver, placenta	BL (hepatocytes)	Chemotherapy: daunorubicin, mitoxantrone, atrasentan, chemotherapy-bile acid conjugates (i.e., Bamet-R2, Bamet-UD2), cytarabine, etoposide, flavopiridol, gimatecan, hydroxyurea, methotrexate, microcystin-LR, carboplatin, cisplatin, oxaliplatin, SN-38 (irinotecan active metabolite), sorafenib- β -D-glucuronide, docetaxel, paclitaxel Other: xenobiotics: olmesartan, valsartan, atrasentan, temocaprilat, pitavastatin, pravastatin, cerivastatin, atorvastatin, rosuvastatin, rifampin, caspofungin, enalapril, BSP, phalloidin, troglitazone, bosentan, benzylpenicillin, nafcillin, some cephalosporins; endogenous: bilirubin, bilirubin-glucuronides, GCA, leukotriene C ₄ , DHEAS, thromboxane B ₂ , T ₄ , T ₃ , PGE ₂ , TCA, E2G, E3S
<i>SLCO1B3</i> (formerly <i>SLC21A8</i>)	OATP1B3 (formerly LST-2, OATP8)	Liver, placenta	BL (hepatocytes)	Chemotherapy: atrasentan, hydroxyurea, methotrexate, microcystin-LR, carboplatin, cisplatin, oxaliplatin, SN-38, docetaxel, paclitaxel, imatinib, sorafenib- β -D-glucuronide Other: xenobiotics: fexofenadine, deltorphin, ouabain, digoxin, rosuvastatin, valsartan, pitavastatin, BSP, rifampin, repaglinide, telmisartan, olmesartan, enalapril, DPDPE; endogenous: bilirubin conjugates, DHEAS, T ₃ , T ₄ , E2G, E3S, GCA, TCA, CCK-8
<i>SLCO2B1</i> (formerly <i>SLC21A9</i>)	OATP2B1 (formerly OATP-B)	Widely expressed: liver, brain (blood-brain barrier), eye, small intestine, heart, kidney, lung, ovary, pancreas, placenta, skeletal muscle, spleen, testis	BL (hepatocytes, ciliary body epithelium); AP (intestine)	Chemotherapy: erlotinib, SN-38 Other: xenobiotics: benzylpenicillin, bosentan, BSP, ezetimibe, fexofenadine, glibenclamide, glyburide, montelukast, statins, sulfasalazine, telmisartan; endogenous: E3S, DHEAS, TCA

AP, apical; Bamet-R2, cis-diamminechloro-cholylglycinate-platinum(II); Bamet-UD2, cis-diammine-bisursodeoxycholate-platinum(II); BL, basolateral; BSP, bromosulfoph-thalein; CCK-8, cholecystokinin octapeptide; DPDPE, [D-penicillamine^{2,5}] encephalin; E2G, estradiol-17 β -glucuronide; GCA, glycocholate; MRI, magnetic resonance imaging; PGE₂, prostaglandin E₂; T₃, triiodothyronine; T₄, thyroxine; TCA, taurocholate.

for OATP1B1 and cholecystokinin octapeptide for OATP1B3—before and after addition of the chemotherapy agent. For OATP1B1, transport of E3S was significantly increased by irinotecan and decreased by paclitaxel and vinblastine; for OATP1B3, transport of cholecystokinin octapeptide was significantly decreased by chlorambucil, paclitaxel, vinblastine, vincristine, mitoxantrone, and etoposide (Marada et al., 2015). This study suggests that the transport of OATP substrates may be affected by coadministration of chemotherapeutic agents with potential implications for clinically significant drug-drug interactions; this is an area that needs further study to assess if clinically relevant concentrations of these

agents affect OATP substrate pharmacokinetics. A preclinical mouse model for such studies has been developed using methotrexate as an OATP substrate (Durmus et al., 2015).

Methotrexate. Methotrexate is an antimetabolite chemotherapy agent whose primary mechanism of action is via inhibition of dihydrofolate reductase, a key enzyme in the folate pathway, leading to termination of DNA synthesis. The methotrexate disposition pathway is complex, with many transporters and enzymes involved (Mikkelsen et al., 2011). While the main path for excretion of methotrexate is renally mediated, it also undergoes hepatic uptake and enterohepatic recirculation, which contribute to its overall disposition

(Walling, 2006). In recent years, variants in genes encoding the hepatic transporters OATP1B1 and OATP1B3 have been found to have a significant effect on methotrexate clearance in several large genome-wide association studies, with OATP1B1 variants having a larger effect than variation in any other gene (Treviño et al., 2009; Ramsey et al., 2012, 2013).

Methotrexate is transported *in vitro* by OATP1B1, OATP1B3 (Abe et al., 2001; van de Steeg et al., 2010; Durmus et al., 2015), and OATP1A2 (Badagnani et al., 2006; van de Steeg et al., 2010). *Oatp1a/1b* deficient mice have significantly higher plasma methotrexate levels and reduced liver methotrexate levels compared with wild type (van de Steeg et al., 2011), with these differences able to be partially or completely rescued by transgenic expression of human OATP1B1, OATP1B3, or OATP1A2 (van de Steeg et al., 2009, 2012). OATP1A2 transport of methotrexate is noted to be both saturable and pH dependent, with 7-fold higher transport in the presence of an acidic extracellular environment (Badagnani et al., 2006). Transport of methotrexate by OATP1B1 and OATP1B3 is inhibited by rifampicin (Durmus et al., 2015).

Taxanes. The taxane chemotherapy agents are mitotic inhibitors that work by disrupting microtubule function. Docetaxel pharmacokinetics are widely variable (Baker et al., 2006), which has clinical implications since reduced clearance is associated with increased risk of dose-limiting toxicities (Bruno et al., 1998, 2003) and clearance may also impact survival (Bruno et al., 2003). There are several differences in the pharmacokinetics of docetaxel and paclitaxel, but both are metabolized by CYP3A4 and other P450 enzymes and are transported by ABCB1, ABCG2, ABCC1, and ABCC2 in addition to OATPs (Baker et al., 2006; Oshiro et al., 2009).

Docetaxel is predominantly dependent on hepatic disposition in humans; ~75% is excreted in bile but only ~5% in urine (Cortes and Pazdur, 1995). Docetaxel is transported *in vitro* by OATP1B3 (Smith et al., 2005; Oshiro et al., 2009; de Graan et al., 2012; Obaidat et al., 2012; Nieuweboer et al., 2014; Yamada et al., 2014; Iusuf et al., 2015; Lee et al., 2015). Significantly decreased docetaxel transport into prostate cancer cells was seen in patient-derived xenografts found to have downregulation of OATP1B3 (de Morré et al., 2016). There are conflicting data for OATP1B1 with some studies showing no transport (Smith et al., 2005; Baker et al., 2009; Yamada et al., 2014) and other more recent studies suggesting that OATP1B1-mediated docetaxel transport occurs (de Graan et al., 2012; Nieuweboer et al., 2014; Lee et al., 2015). Docetaxel is transported by mouse *Oatp1b2* (de Graan et al., 2012; Lee et al., 2015). *Slco1b2* knockout mice show significantly higher plasma levels and decreased liver-to-plasma ratios of docetaxel (Iusuf et al., 2015; Lee et al., 2015). *Oatb1b2*-deficient mice have markedly increased docetaxel area under the plasma time-concentration curve (AUC) (de Graan et al., 2012) and *Oatp1a/1b* knockout mice have higher plasma AUC and reduced liver-to-plasma AUC ratios compared with wild type, with intestinal absorption of docetaxel not affected (Iusuf et al., 2015). Collectively, these data suggest OATP1B transporters are involved in hepatic docetaxel uptake and clearance.

Paclitaxel is transported significantly by OATP1B3 (Smith et al., 2005; Oshiro et al., 2009; Svoboda et al., 2011; Park et al., 2016). There are conflicting data for OATP1B1-mediated transport of paclitaxel, with some negative data

(Smith et al., 2005) and other data showing paclitaxel transport by OATP1B1 *in vitro* and the ability of OATP1B1 or OATP1B3 transfected into cells to improve cytotoxicity of paclitaxel (Svoboda et al., 2011). Paclitaxel is also transported by mouse *Oatp1a/1b* (van de Steeg et al., 2010), with *Slco1a/1b* null mice having higher AUC and lower liver uptake for paclitaxel compared with wild type, and transport was noted to be saturable at the highest doses of paclitaxel (van de Steeg et al., 2011). Human hepatoma HepG2 cells with significantly reduced OATP1B3 expression show paclitaxel resistance (Takano et al., 2009). The clinically used drug vehicle Cremophor inhibits OATP1B3 transport of paclitaxel (Smith et al., 2005), which has the potential to cause drug-drug interactions.

Irinotecan/7-Ethyl-10-Hydroxycamptothecin. Irinotecan is a camptothecin derivative that exerts an antitumor effect by inhibition of topoisomerase I, resulting in double-stranded DNA breaks and cell death. It is spontaneously converted to an active metabolite, 7-ethyl-10-hydroxycamptothecin (SN-38), by hepatic carboxylesterase and butyrylcholinesterase (de Man et al., 2018). SN-38 is believed to play a role in both the efficacy and toxicity associated with irinotecan-containing regimens, especially diarrhea (Kehrer et al., 2001; Fujita et al., 2016). SN-38 is further metabolized to an inactive form, SN-38-glucuronide, by uridine diphosphate glucuronosyltransferases, most prominently by the 1A1 isoform (UGT1A1); this glucuronide form is transported to the intestinal lumen via bile (Lokiec et al., 1995; de Man et al., 2018). Other transporters and enzymes, besides OATPs, involved in irinotecan disposition include ABCB1, ABCC1-2, ABCG2, CYP3A4, and CYP3A5. Irinotecan is primarily eliminated in the bile (66%), but irinotecan and its metabolites can also be found in the urine (de Man et al., 2018).

The parent drug irinotecan does not seem to be a substrate for OATP1B1 (Nozawa et al., 2005a; Oostendorp et al., 2009; Iusuf et al., 2014) or OATP1B3 (Iusuf et al., 2014), but these transporters are important for disposition of the active metabolite SN-38 (Yamaguchi et al., 2008; Oostendorp et al., 2009; Obaidat et al., 2012; Fujita et al., 2014). OATP1B1 does not transport SN-38 glucuronide (Nozawa et al., 2005a). OATP2B1 transports SN-38 in *Xenopus* oocytes (Fujita et al., 2016), but not in HEK293 cells (Fujita et al., 2014). *Oatp1a/1b* null mice have markedly increased plasma exposure of irinotecan and SN-38 and significantly decreased liver-to-plasma ratios of these compounds compared with wild type. When the human transporters OATP1B1 or OATP1B3 were introduced into these mice, SN-38 plasma levels reverted to the same levels as in the wild-type mice; however, irinotecan plasma levels were not affected, suggesting that SN-38, but not irinotecan, is a substrate for OATP1B1 and OATP1B3 *in vivo* (Iusuf et al., 2014).

Gastrointestinal toxicity (such as diarrhea) is the most common dose-limiting side effect of irinotecan and is due to SN-38 accumulation in intestinal tissues (Fujita et al., 2016). SN-38 is transported by OATP2B1 (Fujita et al., 2016) which is expressed in the intestines (Tamai, 2012). OATP2B1-mediated SN-38 transport is inhibited by apple juice (in a dose-dependent manner) and cefixime, among other compounds, with mice given apple juice concurrently with SN-38 having less gastrointestinal toxicity than control mice (Fujita et al., 2016). Additionally, the concurrent use of cyclosporine (a known potent OATP inhibitor) to reduce biliary excretion of irinotecan metabolites (through

various transporters) has been shown to improve the toxicity profile of irinotecan in patients with metastatic colon cancer (Chester et al., 2003); the concept of utilizing an OATP inhibitor to alter the pharmacokinetic parameters of chemotherapeutic agents is an area that warrants additional investigation.

Tyrosine Kinase Inhibitors. Tyrosine kinase inhibitors (TKIs) are chemotherapy agents that disrupt cell signaling via inhibition of tyrosine kinases. There are numerous TKIs in routine clinical use that have slightly different pharmacokinetic properties, but all are transported into and out of cells by various members of the solute carrier and ATP-binding cassette (ABC) families and are primarily metabolized by various P450 enzymes (Neul et al., 2016; Gong et al., 2017). Transport of TKIs by OATPs has been the subject of many recent studies (Hu et al., 2008, 2009, 2014; Yamakawa et al., 2011; Obaidat et al., 2012; Zimmerman et al., 2013; Vasilyeva et al., 2015; Bins et al., 2017; Bauer et al., 2018). In general, elimination of TKIs is primarily hepatic and mediated by P450 enzymes (O'Brien and Moghaddam, 2017), with renal clearance playing a small role for some agents (van Erp et al., 2009).

Erlotinib is transported by OATP2B1 in vitro (Bauer et al., 2018). Sorafenib transport by OATP1B1 was negative in some studies (Hu et al., 2009; Bins et al., 2017), but another study showed that OATP1B1- and OATP1B3-transfected cells transported sorafenib significantly higher than vector control in vitro. However, the in vivo mouse data showed no difference in sorafenib pharmacokinetics between wild-type and *Oatp1b2*-deficient mice, and no change in sorafenib transport in humanized OATP1B1 or OATP1B3 mice compared with *Oatp1a/b* null mice (Zimmerman et al., 2013). Sorafenib is not transported by OATP1A2 or OATP1B3 (Hu et al., 2009). Sorafenib has an important metabolite, sorafenib- β -D-glucuronide, which is transported into hepatocytes by OATP1B1 (Bins et al., 2017) and mouse *Oatp1a/1b* (Vasilyeva et al., 2015). In contrast to the sorafenib data in the Zimmerman et al. (2013) study, sorafenib- β -D-glucuronide transport was affected in *Oatp1b2* deficient or *Oatp1a/1b* null mice with these mice having significantly higher sorafenib- β -D-glucuronide plasma AUC compared with wild type, and this difference in AUC partially corrected to wild type in mice transgenic for human OATP1B1 or OATP1B3. The Zimmerman et al. (2013) data overall suggest that in vivo OATP1B1 and OATP1B3 are not important for sorafenib transport but are important for transport of its glucuronide metabolite. Imatinib is transported by OATP1A2 and OATP1B3 (Hu et al., 2008; Yamakawa et al., 2011; Obaidat et al., 2012). However, while imatinib transport by OATP1A2 is seen in vitro, imatinib absorption in cancer patients was not found to be associated with function-altering OATP1A2 variants or with coadministration of rosuvastatin (a known OATP1A2 inhibitor), suggesting that an alternate transport pathway may also be important in vivo (Echoute et al., 2011).

TKIs also have implications in drug-drug interactions involving OATPs. Sorafenib and other TKIs (axitinib, nilotinib, pazopanib, and lapatinib) are inhibitors of OATP1B1 in vitro; however, in vivo data are conflicting and it is likely that transport through other mechanisms becomes important when OATP1B1 is inhibited in these cases (Polli et al., 2008; Hu et al., 2014). Coadministration of sorafenib changes the pharmacokinetics of docetaxel, a known OATP substrate, which may have clinical implications since sorafenib is being

incorporated into protocols for many different solid tumors due to its favorable side effect profile and efficacy against these tumors (Awada et al., 2012).

Anthracyclines. The anthracyclines, including doxorubicin, daunorubicin, and mitoxantrone, have several mechanisms that contribute to cytotoxicity: disruption of DNA and RNA synthesis via intercalation, inhibition of topoisomerase II, generation of free oxygen radicals, and interference with histone function. Approximately 50% of doxorubicin's disposition is mediated by biliary elimination, suggesting hepatic uptake and clearance play important roles in its disposition (Danesi et al., 2002). Multiple transporters are involved in doxorubicin disposition, including uptake by SLC22A16 and efflux by ABCC1, ABCG2, and ABCB1. It also undergoes metabolism via several pathways (Thorn et al., 2011).

Recent studies have evaluated the role of OATPs in doxorubicin disposition (Durmus et al., 2014; Lee et al., 2017). Doxorubicin uptake and transport by OATPs in vitro vary according to the model system that is used. Doxorubicin is transported by OATP1A2-expressing HEK293 (Durmus et al., 2014), HeLa, and Madin-Darby canine kidney II cells (Lee et al., 2017), while OATP1B1- and OATP1B3-mediated doxorubicin transport is seen in Madin-Darby canine kidney II cells (Lee et al., 2017) but not in HeLa (Lee et al., 2017) or HEK293 cells (Durmus et al., 2014). Results of in vivo studies in rodents have shown that doxorubicin uptake and disposition are significantly decreased in *Oatp1a/1b* null mice compared with wild type (Durmus et al., 2014; Lee et al., 2017) and that transgenic expression of human OATPs either completely (for OATP1A2) or partially (for OATP1B1 and OATP1B3) reverts doxorubicin pharmacokinetics to wild-type values (Durmus et al., 2014). These data together suggest that OATP1A2, OATP1B1, and OATP1B3 are all involved in doxorubicin transport. The related agents daunorubicin and mitoxantrone are transported by OATP1B1 in vitro, and deficiency of mouse *Oatp1b2* results in significantly increased plasma AUC of both drugs (Drenberg et al., 2016).

Platins. The platinum chemotherapy agents work by cross-linking DNA and therefore disrupting DNA synthesis and repair. These compounds are transported by *SLC31A1*, ABCG2, ABCG2, and MDR1 (P-glycoprotein) (Marsh et al., 2009; Dasari and Tchounwou, 2014), and importantly by organic cation transporters (OCTs), OCT1, OCT2, and OCT3, encoded by *SLC22* genes (Wagner et al., 2016). A number of enzymes are involved in converting platinum-based chemotherapy drugs to inactive metabolites, such as myeloperoxidase and superoxide dismutase (Marsh et al., 2009). The elimination of platinum agents is almost exclusively through the kidneys (Burger et al., 2011).

Cisplatin, carboplatin, and oxaliplatin are transported in vitro by OATP1B1 and OATP1B3, and cytotoxicity of these agents in human tumor cells was found to be enhanced with increasing OATP1B3 mRNA expression (Lancaster et al., 2013). *Oatp1b2* knockout mice have significantly reduced liver-to-plasma ratios of cisplatin compared with wild type (Lancaster et al., 2013). Bile acid-cisplatin derivatives have been developed as liver-trophic drugs that could become concentrated in bile and help overcome resistance to platinum agents (Criado et al., 1997, 2000). Two of these, Bamet-R2 (cis-diamminechloro-cholylglycinate-platinum(II)) and Bamet-UD2 (cis-diammine-bisursodeoxycholate-platinum(II)), are transported by OATP1B1 and to a lesser extent by OATP1A2 (Briz et al., 2002).

Summary: OATPs in Chemotherapy Disposition. While a growing number of chemotherapeutic agents have been shown to be OATP substrates *in vitro*, it remains yet to be determined if OATPs are important to the clinical pharmacology of all these purported anticancer agents. However, a series of follow-up or complementary studies in animal models using Oatp knockout mice or transgenic human OATP mice have suggested OATP transporters are important to the clinical pharmacology of agents such as methotrexate, taxanes, and anthracyclines. Additional studies to evaluate the roles of OATP transporters in chemotherapy disposition are warranted due to the narrow therapeutic indices associated with them in cancer therapeutics. A more comprehensive evaluation and understanding of the clinical pharmacology of these drugs would yield important knowledge to better optimize chemotherapy dosing and combination therapies that may improve therapeutic efficacy while mitigating serious drug-mediated adverse effects.

Pharmacogenetics of OATP Transporters

The *SLCO* genes are polymorphic, with common (minor allele frequency >5%) variants identified in OATP1B1, OATP1B3, and OATP1A2. Some of these variants affect the expression, localization, and/or function of the transporter and can significantly alter the disposition of xenobiotics and endogenous substrates (Konig, 2011). Table 2 contains information on functional consequences of selected polymorphisms in *SLCO1A2*, *SLCO1B1*, *SLCO1B3*, and *SLCO2B1*, and this topic was also reviewed in detail recently (Zhou et al., 2017).

OATP1A2. Multiple function-altering variants in *SLCO1A2* have been reported (Lee et al., 2005; Zhou et al., 2015). Several *SLCO1A2* variants show altered transport of methotrexate, including the hyperfunctional c.38T>C variant, hypofunctional c.516A>C, and c.502C>T variants, and nonfunctional c.833delA variant (Badagnani et al., 2006). The c.516A>C variant has been reported as hypofunctional for other substrates as well, and some *SLCO1A2* variants have substrate-specific alteration of transport (Lee et al., 2005). Imatinib clearance is significantly affected by several single nucleotide polymorphisms (SNPs) in *SLCO1A2*, with patients carrying at least one copy of each of the intronic variants c.-1167G>A and c.-1094G>A having significantly reduced drug clearance compared with wild type, and patients who do not have the intronic variant c.-423G>A (homozygous wild type) have increased clearance (Yamakawa et al., 2011). The clinical significance of altered drug transport function associated with *SLCO1A2* variants has not been determined to date. Further study of *SLCO1A2* variation as it relates to chemotherapy disposition will be helpful in the future given this transporter's role at the blood-brain barrier and the importance of developing chemotherapeutic agents that penetrate the brain tissue for certain diagnoses, most notably malignant brain tumors.

OATP1B1. *SLCO1B1* variants have been widely studied with regard to impact on the pharmacokinetics of many drugs (Niemi et al., 2011; Shitara, 2011), and notably in the incidence of adverse drug reactions in patients treated with statins (Link et al., 2008; Jiang et al., 2016). The *SLCO1B1* c.521T>C variant, which has a minor allele frequency of 12%–18% in European and East Asian populations with lower frequency (1.9%) in sub-Saharan African populations (Pasanen et al.,

2008), has been the most extensively studied of the *SLCO1B1* variants and is associated with significantly impaired hepatic uptake, and thus corresponding increased plasma levels, of many substrates (Tirona et al., 2001; Nishizato et al., 2003; Mwinyi et al., 2004; Niemi et al., 2004, 2005a,b; Kameyama et al., 2005; Nozawa et al., 2005a; Katz et al., 2006; Ho et al., 2007; Zhang et al., 2007; Xiang et al., 2009). The c.521T>C variant has been identified as a significant risk factor for statin-induced myopathy (Link et al., 2008) and other statin-induced adverse drug reactions (Jiang et al., 2016). A case-control analysis of patients in a large randomized trial study on the effectiveness of additional reductions in cholesterol and homocysteine found an odds ratio for myopathy of 4.5 per copy of the variant C allele, and homozygous variant (CC) patients had an odds ratio of 16.9 for development of myopathy compared with TT patients (Link et al., 2008). Another commonly studied *SLCO1B1* variant is the c.388A>G variant (Tirona et al., 2001), which has no apparent relationship with statin adverse drug reactions (Jiang et al., 2016).

Several *SLCO1B1* haplotypes with differential drug transport compared with wild type have been identified. *SLCO1B1**1a is the reference allele, with the *1b haplotype including the c.388A>G variant, the *5 haplotype having the c.521T>C variant, and the *15 haplotype containing both the c.388A>G and c.521T>C variants (Tirona et al., 2001). There are conflicting data regarding the function of the *1b haplotype, with transport of some substrates being no different compared with transport by the wild-type protein (Tirona et al., 2001; Michalski et al., 2002; Nozawa et al., 2002; Iwai et al., 2004; Lee et al., 2015), while in other studies it appears to be hyperfunctional for some substrates (Michalski et al., 2002; Mwinyi et al., 2004; Ieiri et al., 2009; Nies et al., 2013; Crona et al., 2016; Drenberg et al., 2016) and hypofunctional for others (Michalski et al., 2002; Drenberg et al., 2016). Some data suggest that the c.388A>G variant causes increased expression of OATP1B1 at the plasma membrane (Nozawa et al., 2002; Nies et al., 2013). The *5 and *15 haplotypes are hypofunctional, including significantly reduced *in vitro* transport of cytarabine, daunorubicin, etoposide, mitoxantrone (Drenberg et al., 2016), and docetaxel (de Graan et al., 2012; Lee et al., 2015). However, in a clinical study, no effect on docetaxel clearance was found for patients carrying the *SLCO1B1* variants g.21130388G>A (promoter variant), c.388A>G, or c.521T>C compared with wild type (de Graan et al., 2012).

The effect of other *SLCO1B1* variants on chemotherapy disposition has been studied. Several studies have examined the relationship between *SLCO1B1* genotype and the high interpatient variability seen in methotrexate clearance (Treviño et al., 2009; Lopez-Lopez et al., 2011; Ramsey et al., 2012, 2013). In 115 pediatric leukemia patients, those who were homozygous for the intronic *SLCO1B1* variant c.1865+248G>A or c.1865+4846T>C had significantly higher plasma methotrexate levels following high-dose methotrexate therapy compared with patients with the wild-type or heterozygous variant genotypes, although the number of patients homozygous for these variants was low. High methotrexate plasma levels at 72 hours after the start of infusion were significantly correlated with development of global toxicity, vomiting, and renal toxicity, suggesting genetic variants that affect methotrexate plasma levels may also increase rates of methotrexate-associated toxicities (Lopez-Lopez et al., 2011).

TABLE 2

Pharmacogenomics of OATPs: selected variants and functional consequences

In vitro and in vivo functional studies as well as pharmacokinetic-pharmacogenetic correlative studies were included in the literature review for this table.

Gene	Nucleotide Change	Amino Acid Change	rs Number	Functional Consequence ^a	Reference	
<i>SLCO1A2</i>	c.-1167G>A	Intronic	rs4148977	Decreased imatinib clearance	Yamakawa et al. (2011)	
	c.-1094G>A	Intronic	rs4148978	Decreased imatinib clearance		
	c.-423G>A	Intronic	rs3764043	Increased imatinib clearance		
	c.38T>C	Ile13Thr	rs10841795	Increased transport of multiple substrates including methotrexate	Badagnani et al. (2006), Gong and Kim (2013)	
	c.404A>T	Asn135Ile	rs45502302	Decreased transport		
	c.502C>T	Arg168Cys	rs11568564	Decreased transport of multiple substrates including methotrexate	Badagnani et al. (2006), Gong and Kim (2013)	
	c.516A>C	Glu172Asp	rs11568563	Decreased transport of multiple substrates including methotrexate		
	c.559G>A	Ala187Thr	rs750165758	Decreased transport	Lee et al. (2005)	
	c.833delA	Asn278Met	rs11568555	Decreased transport of multiple substrates including methotrexate	Badagnani et al. (2006)	
	<i>SLCO1B1</i>	g.21130388G>A	Intronic	rs4149015	Decreased transport of multiple substrates including SN-38	Niemi et al. (2004), Han et al. (2008)
c.217T>C (*2)		Phe73Leu	rs56101265	Decreased transport of multiple substrates including docetaxel	Tirona et al. (2001), Gong and Kim (2013), Lee et al. (2015)	
c.245T>C		Val82Ala	rs56061388	Decreased transport	Tirona et al. (2001), Gong and Kim (2013)	
c.388A>G (*1b)		Asn130Asp	rs2306283	Decreased transport of some substrates including cytarabine; increased or unchanged transport for other substrates	Kameyama et al. (2005), Han et al. (2008), Gong and Kim (2013), Drenberg et al. (2016)	
c.467A>G		Glu156Gly	rs72559745	Decreased transport	Tirona et al. (2001), Gong and Kim (2013)	
c.521T>C (*5)		Val174Ala	rs4149056	Decreased transport of multiple substrates including SN-38, docetaxel, cytarabine, etoposide, mitoxantrone, and daunorubicin; decreased clearance of methotrexate	Tirona et al. (2001), Kameyama et al. (2005), Nozawa et al. (2005a), Han et al. (2008), Gong and Kim (2013), Ramsey et al. (2013), Lee et al. (2015), Drenberg et al. (2016)	
c.578T>G		Leu193Arg	rs72559746	Decreased to abolished transport of some substrates	Michalski et al. (2002), Gong and Kim (2013)	
c.1007C>G		Pro336Arg	rs72559747	Decreased for some substrates, unchanged for others	Nishizato et al. (2003), Gong and Kim (2013)	
c.1058T>C		Ile353Thr	rs55901008	Decreased transport	Tirona et al. (2001), Gong and Kim (2013)	
c.1294A>G		Asn432Asp	rs56387224	Decreased transport		
c.1463G>C		Gly488Ala	rs59502379	Decreased transport of multiple substrates including docetaxel	Tirona et al. (2001), Gong and Kim (2013), Lee et al. (2015)	
c.1964A>G		Asp655Gly	rs56199088	Decreased transport	Tirona et al. (2001), Gong and Kim (2013), Lee et al. (2015)	
c.2000A>G		Glu667Gly	rs55737008	Decreased transport	Tirona et al. (2001), Gong and Kim (2013)	
c.1865+248G>A		Intronic	rs4149081	Decreased methotrexate clearance	Treviño et al. (2009), Ramsey et al. (2013)	
c.1865+4846T>C		Intronic	rs11045879	Decreased methotrexate clearance		
<i>SLCO1B3</i>	c.1599-5676A>G	Intronic	rs11045585	Decreased or unchanged docetaxel clearance	Chew et al. (2011), de Graan et al. (2012)	
	c.439A>G	Thr147Ala	rs57585902	Decreased or unchanged docetaxel transport	Baker et al. (2009), Chew et al. (2011), Lee et al. (2015)	
	c.699G>A	Met233Ile	rs7311358	Decreased transport of multiple substrates including paclitaxel	Schwarz et al. (2011), Gong and Kim (2013), Park et al. (2016)	
	c.1559A>C	His520Pro	rs559692629	Decreased transport of multiple substrates; decreased or unchanged docetaxel transport	Baker et al. (2009), Chew et al. (2011), Schwarz et al. (2011), Lee et al. (2015)	
	c.1564G>T	Gly522Cys	rs72559743	Decreased transport	Letschert et al. (2004), Gong and Kim (2013)	
	c.1679T>C	Val560Ala	rs12299012	Decreased transport of multiple substrates; decreased or unchanged docetaxel transport	Baker et al. (2009), Chew et al. (2011), Schwarz et al. (2011), Gong and Kim (2013), Lee et al. (2015)	
	<i>SLCO2B1</i>	c.601G>A	Val201Met	rs35199625	Decreased transport	Ho et al. (2006)
		c.1175C>T	Thr392Ile	rs1621378	Decreased transport	Nozawa et al. (2002), Gong and Kim (2013)
c.1457C>T		Ser486Phe	rs2306168	Decreased transport	Nozawa et al. (2002), Gong and Kim (2013)	
c.1526G>A		Arg509His	rs140407559	Decreased transport	(Nozawa et al. (2002))	

^aIncreased and decreased refer to transport function of the variant transporter compared with the corresponding wild-type transporter. For some variants, effect on transport function varies by substrate; in these cases, the predominant effect on transporter function is listed.

A large clinical study (Treviño et al., 2009) and a follow-up study including additional patients (Ramsey et al., 2013), which utilized a genome-wide association study approach, found that SNPs in *SLCO1B1* were significantly associated with methotrexate clearance. The *SLCO1B1* variants c.1865+248G>A and c.1865+4846T>C were in linkage disequilibrium with each other and with c.521T>C, all of which were associated with decreased methotrexate clearance (Treviño et al., 2009).

Interestingly, those carrying wild-type alleles at these positions had increased incidence of gastrointestinal toxicity (per National Cancer Institute Cancer Therapy Evaluation Program toxicity grading) compared with those with variant alleles, presumably due to enhanced clearance and resultant lower plasma exposure with corresponding higher gastrointestinal tract methotrexate exposure via elimination pathways. In the follow-up study, the SNP most

significantly associated with methotrexate clearance was c.521T>C, in which homozygous variant (CC) patients had methotrexate clearance that was on average 13% lower than homozygous wild-type (TT) patients. This genotype explained 2% of the variation in methotrexate clearance; a higher proportion explained than that for age and sex combined. In this study, three other significant SNPs in *SLCO1B1* were in significant linkage disequilibrium with c.521T>C (Ramsey et al., 2013). Another study utilizing the same patient population indicated that, after controlling for c.521T>C, 15 additional SNPs in *SLCO1B1*, all nonsynonymous and some rare (minor allele frequency <5%), were significantly associated with methotrexate clearance, with these SNPs either causing increased or decreased clearance compared with wild type. These data showed that even rare damaging SNPs can have a significant impact on methotrexate clearance (Ramsey et al., 2012).

A separate study replicated the finding that c.1865+248G>A and c.1865+4846T>C are associated with methotrexate disposition; in this study, these variants were associated with higher average plasma methotrexate levels, including levels above the upper limit of the desired range (Li et al., 2015). A recent study in adult patients with hematologic malignancies receiving high-dose methotrexate suggests patients with the *SLCO1B1* variant c.388A>G or c.521T>C exhibit differential urinary endogenous metabolomic profiles that may interact with renal organic anion transporters to modulate risk for methotrexate-induced toxicities, illustrating the link between *SLCO1B1* SNPs and methotrexate clearance and/or toxicity may be multifactorial and more complex than previously thought (Martinez et al., 2018).

Regarding irinotecan and SN-38 disposition, *Xenopus* oocytes expressing the *SLCO1B1**15 allele showed markedly reduced transport for SN-38, while the *5 allele conferred a more modest reduction in SN-38 transport (Nozawa et al., 2005a). Patients with the *15 haplotype had 3-fold reduction in irinotecan clearance and significantly higher AUC for both irinotecan and SN-38 compared with *1a/*1a (Xiang et al., 2006). In patients with nonsmall cell lung cancer treated with irinotecan and cisplatin, the *SLCO1B1* variants c.521T>C and g.21130388G>A were found to affect the pharmacokinetics of SN-38. Patients carrying at least one copy of the c.521T>C variant allele or those homozygous for the g.21130388G>A promoter variant had a significantly higher AUC of the important irinotecan metabolite SN-38 compared with wild-type patients. Additionally, SN-38 clearance was significantly lower in the g.21130388AA patients and there was a trend toward lower clearance in patients with at least one copy of the c.521T>C variant. None of the variants in this study were associated with tumor response or pharmacokinetics of the parent drug irinotecan (Han et al., 2008). However, in another study, the *SLCO1B1**5 haplotype was associated with significantly increased irinotecan AUC, but neither the *SLCO1B1**1b nor the *SLCO1B1**5 haplotype was associated with SN-38 pharmacokinetics (Innocenti et al., 2009). In a study by Crona et al. (2016), the c.521T>C variant was associated with increased irinotecan AUC in a discovery cohort of patients; however, this finding did not replicate in a validation cohort, and this variant was not associated with SN-38 pharmacokinetics. Thus, the relationship between these *SLCO1B1* variants and the pharmacokinetics of irinotecan and SN-38 is not consistently defined and warrants

further study in larger populations of patients to determine whether *SLCO1B1* variants influence irinotecan and/or SN-38 pharmacokinetics.

However, *SLCO1B1* variants have been linked to irinotecan-induced toxicities. The *SLCO1B1* c.521T>C variant was associated with increased risk of irinotecan-induced grade 3/4 neutropenia in a cohort of adult Japanese patients with various cancers who were treated either with irinotecan monotherapy or irinotecan plus cisplatin (Sai et al., 2010). A patient with the *SLCO1B1**15/15 genotype as well as another at-risk genotype was reported to have excessive accumulation of SN-38 in the plasma circulation, which led to life-threatening diarrhea and neutropenia (Takane et al., 2009). Patients with at least one copy of the c.521T>C variant allele who were treated with irinotecan had higher rates of grade 4 neutropenia compared with wild type, and patients homozygous for the c.388A>G variant, had higher rates of grade 3 diarrhea following irinotecan therapy (Han et al., 2008). In advanced cancer patients treated with single-agent irinotecan, the *SLCO1B1**1b haplotype was associated with a lower absolute neutrophil count nadir when comparing *1b/1b patients to *1a/1a or *1a/1b patients (Innocenti et al., 2009); conversely, the c.388A>G variant was associated with a protective effect against neutropenia following irinotecan therapy in another study (Crona et al., 2016). With regard to outcomes, patients with the c.521T>C variant had increased SN-38 exposure compared with wild type, and those with the *SLCO1B1* c.388GG genotype had significantly longer progression-free survival compared with the c.388AA genotype (Teff et al., 2015). Collectively, these genetic association studies demonstrate that *SLCO1B1* variation may play an important role in the interindividual variability in chemotherapy disposition and response for several OATP1B1 chemotherapeutic substrates.

OATP1B3. The functional consequences of various *SLCO1B3* variants, especially c.334T>G and c.699G>A, have been studied, for which there are substrate-specific alterations in transport compared with wild type (Letschert et al., 2004; Schwarz et al., 2011). OATP1B3 transports testosterone in vitro, and cells expressing OATP1B3 containing either the c.334T>G or c.699G>A variant transported testosterone at a similar rate compared with wild type, while the presence of both variants concurrently resulted in significant impairment of testosterone transport (Hamada et al., 2008). This has potential implications for the growth of hormone-dependent tumors such as prostate cancer.

Several *SLCO1B3* variants have been found to affect docetaxel transport compared with wild type, including c.699G>A, c.1559A>C, c.1679T>C, and the haplotype containing c.334T>G and c.699G>A in vitro (Lee et al., 2015); however, results from clinical studies on the effect of *SLCO1B3* variants on docetaxel elimination are mixed. In a study on the effect of the *SLCO1B3* haplotype on docetaxel pharmacokinetics in cancer patients, the variants c.359+76G>A (intronic), c.699G>A, c.1599-5676A>G (intronic), and c.*347_*348insA were used to construct haplotypes that had a significant impact on docetaxel clearance and AUC. These haplotypes explained 29% and 22% of the variability in docetaxel clearance and AUC, respectively; specifically, one haplotype resulted in a 30% decrease in clearance and 40% increase in AUC, while another haplotype increased clearance by 50% compared with the reference haplotype

(Chew et al., 2012). However, in a study on patients treated with docetaxel, no relationship was found between the c.699G>A, c.1559A>C, c.1679T>C, c.334T>G, c.439A>G, or c.767G>C variant and docetaxel pharmacokinetics (Baker et al., 2009). Patients with nasopharyngeal carcinoma who were homozygous for the intronic *SLCO1B3* variant c.1599-5676A>G had significantly higher AUC and lower clearance of docetaxel in one study, while multiple other *SLCO1B3* variants (including c.334T>G, c.1559A>C, c.1679T>C, c.699G>A, and c.1599-5676A>G) had no effect on docetaxel pharmacokinetics, although the number of patients with these variants in this study was low (Chew et al., 2011). Another study similarly found no effect of the variants c.334T>G, c.699G>A, and c.1599-5676A>G on docetaxel clearance (de Graan et al., 2012).

Taxane-induced transport and toxicities have been studied with respect to *SLCO1B3* variation. For paclitaxel, significantly reduced transport was found for oocytes expressing the c.699A>G variant, while no effect on paclitaxel transport was found for the c.334A>G variant (Park et al., 2016). A clinical study found no relationship between paclitaxel-associated neurotoxicity and the *SLCO1B3* variants c.334T>G and c.699G>A in 118 cancer patients after adjusting for age and treatment schedule (Leskelä et al., 2011). The c.1599-5676A>G variant in *SLCO1B3* has been associated with grade 3/4 docetaxel-induced leukopenia and neutropenia in some studies (Kiyotani et al., 2008; Yamada et al., 2014), but had no effect on these toxicities or other hematologic abnormalities in another study (Choi et al., 2015). Thus, the consequences of *SLCO1B3* variation to taxane-induced differential transport or risk for drug-mediated toxicity have not as yet been clearly defined.

OATP Expression in Tumor Tissues and Their Potential as Therapeutic Targets

The differential expression of OATPs in cancerous versus normal tissues has been studied as a way to develop novel diagnostic or therapeutic strategies for these tumors (Okabe et al., 2008). OATPs that are highly expressed in cancerous tissues with little to no expression in corresponding normal tissues may be useful as diagnostic markers and/or therapeutic targets, since malignant tissues that have upregulation of OATPs transporting chemotherapeutic substrates may be more sensitive to the cytotoxic effects of these agents.

This makes screening for OATP expression prior to starting therapy an attractive way to increase the chance of response to a chemotherapy regimen (Buxhofer-Ausch et al., 2013). Table 3 contains information on the overexpression of OATP1A2, OATP1B1, OATP1B3, and OATP2B1 in various cancer tissues, which has recently been reviewed in more detail (Thakkar et al., 2015).

While OATP1B3 is predominantly expressed in liver under normal conditions, it has been detected in various malignant tissues including tumors of the cervix, intestines, liver, lung, pancreas, and genitourinary tract (Lancaster et al., 2013). A cancer-specific form of OATP1B3, also referred to as cancer-type OATP1B3, has been identified in which an alternative splice site is used, resulting in a protein that is structurally different from that found in normal liver; the cancer-specific OATP1B3 transcript has been detected in malignant tissues from the colon (Nagai et al., 2012; Han et al., 2013; Thakkar et al., 2013; Sun et al., 2014), pancreas (Han et al., 2013; Thakkar et al., 2013), and lung (Nagai et al., 2012; Sun et al., 2014). Some commonly used detection methods for wild-type OATP1B3 do not detect this cancer-specific OATP1B3; therefore, studies that do not show expression of OATP1B3 in cancerous tissues must be interpreted with caution if they did not search for the cancer-specific variant (Evangelini et al., 2017). The transport function of the cancer-specific OATP1B3 variant for at least some substrates is significantly decreased or abolished (Thakkar et al., 2013; Sun et al., 2014), although transport of other substrates is similar to that of the wild-type transporter (Imai et al., 2013).

Additionally, OATP1A2, OATP1B1, OATP1B3, and OATP2B1 transport many endogenous steroid hormones and hormone conjugates including estradiol, E3S, and dehydroepiandrosterone sulfate (DHEAS) (Kullak-Ublick et al., 1998, 2001; König et al., 2000; Cui et al., 2001; Tamai et al., 2001; Pizzagalli et al., 2003; Nozawa et al., 2004a,b; Grube et al., 2006a; Miyagawa et al., 2009; Maeda et al., 2010; De Bruyn et al., 2011; Yang et al., 2011; Buxhofer-Ausch et al., 2013). Steroid hormones and their conjugates are important for the proliferation of tumor cells in hormone-dependent malignancies (Nozawa et al., 2004b, 2005b; Hamada et al., 2008; Hong and Chen, 2011). However, there is generally redundant transport of these hormones by one or more OATPs in addition to other transporters; for example, in one study OATP1B3 transported E3S efficiently but only accounted for 6% of total E3S transport in breast cancer cells (Maeda et al., 2010). The expression of OATPs in hormone-dependent cancers has been

TABLE 3
Differential OATP protein expression in cancer tissues
See the text for references for this table.

Protein	Malignant Tissue Distribution ^a
OATP1A2	Increased expression: breast, pancreas, bone, some lung cancer cell lines Decreased expression: colon, some lung cell lines
OATP1B1	Increased expression: breast, pancreas, prostate, ovary, lung, colon Decreased expression: liver
OATP1B3	Increased expression: colon, pancreas, lung, breast, prostate, ovary, lung, stomach, gallbladder Decreased expression: liver
OATP2B1	Increased expression: lung (conflicting evidence), breast, colon, bone Decreased expression: none reported

^aIncreased and decreased refer to expression of the transporter in malignant tissue compared with normal tissue of the same type.

studied and linked to the level of differentiation in the tumor specimens, which may be used as a marker of disease stage (Pressler et al., 2011).

Breast Tumors. OATP1A2, OATP1B1, OATP1B3, and OATP2B1 have all been found in breast cancer cells at levels similar to or higher than those found in normal breast tissue (Pizzagalli et al., 2003; Al Sarakbi et al., 2006; Bleasby et al., 2006; Miki et al., 2006; Muto et al., 2007; Meyer zu Schwabedissen et al., 2008; Kindla et al., 2011; Banerjee et al., 2012; Stute et al., 2012; Buxhofer-Ausch et al., 2013). Treatment with chemotherapy changes the expression levels of these transporters in a cell line-dependent manner (Stute et al., 2012). Hormone-dependent breast tumor cells have been shown to have increased transport of E3S compared with hormone-independent tumors, possibly due to increased OATP expression in hormone-dependent tumors (Banerjee et al., 2012–2014).

Estrogens are important for development and growth of hormone-dependent breast cancers, with certain estrogen derivatives being taken up into tumor cells to be converted to their active forms in situ (Hong and Chen, 2011). Estrogen concentrations in tumors have been found to be significantly higher than levels in the plasma circulation, suggesting an active process resulting in accumulation of intratumoral estrogens (Pasqualini et al., 1996). E3S is an important source of estrogen for breast cancer cells and is found at particularly high levels in postmenopausal breast cancer patients (Pasqualini et al., 1996). E3S is converted to estradiol in a series of enzymatic reactions, and estradiol drives cell proliferation (Nozawa et al., 2004b, 2005b; Banerjee et al., 2013; Matsumoto et al., 2015). E3S transport into breast cancer cells is apparently by an active carrier-mediated process given its uptake kinetics (Nozawa et al., 2004b). Due to their transport of steroid hormones, OATPs have been considered important to proliferation in breast cancer cells (Banerjee et al., 2012).

OATP-mediated transport of hormone conjugates may be useful as a therapeutic target (Banerjee et al., 2012). A study examining the plasma levels of estrone, estrone conjugates, and androstenedione in postmenopausal women with resected early stage estrogen receptor positive breast cancer (prior to aromatase inhibitor therapy) found that several genetic variants in *SLCO1B1*, including c.521T>C and c.463C>A, were associated with higher levels of these hormones compared with wild type. This is clinically relevant because estrone conjugates are converted to estrone by the enzyme steroid sulfatase, and steroid sulfatase inhibitors are available for clinical use (Dudakov et al., 2017). Additionally, expression of OATPs in tumor specimens may be associated with disease prognosis. Overexpression of OATPs has also been associated with higher tumor grade (Al Sarakbi et al., 2006; Matsumoto et al., 2015). However, increased OATP expression may also make breast tumors more susceptible to chemotherapeutic agents that are transported by that OATP, as was suggested in a study where OATP1B3 expression was associated with improved prognosis in estrogen receptor positive patients only, possibly due to increased uptake of tamoxifen in these patients (Muto et al., 2007). Recently, it has been shown that OATP1A2 expression may predict pathologic response to neoadjuvant chemotherapy in triple-negative breast cancer patients as well (Hashimoto et al., 2014).

Prostate and Other Genitourinary Tumors. Prostate cancer specimens have been found to have increased protein

and/or mRNA expression of OATP1B1 (Buxhofer-Ausch et al., 2013) and OATP1B3 (Hamada et al., 2008; Pressler et al., 2011; Buxhofer-Ausch et al., 2013; Lancaster et al., 2013) compared with normal prostate or benign prostatic hyperplasia specimens. Increased OATP1B3 expression has been correlated with increased tumor grade (Pressler et al., 2011). OATP1B1 and OATP1B3 expression is increased in metastatic lesions from prostate cancer that has not responded to androgen deprivation therapy compared with untreated prostate cancer (Wright et al., 2011).

Androgen-depleting therapies are the current mainstay of treatment of prostate cancer; however, over time, many patients become resistant to this therapy and progress to castration-resistant prostate cancer, which can be fatal (Cho et al., 2014). Upregulation of some OATPs is also believed to allow prostate cancer cells to continue to grow by more effectively scavenging low levels of circulating androgens and other steroids such as E3S during androgen-depleting therapies; therefore, therapies to reduce OATP-mediated steroid hormone transport could represent a treatment strategy for resistant prostate cancer (Cho et al., 2014). The adrenal steroid hormone DHEAS, which is not affected by androgen-depleting therapies, has also been considered as a possible pharmacological target given its role in cell proliferation under androgen-depleted conditions, which can cause tumor resistance to antiandrogen therapies (Evaul et al., 2010; Arakawa et al., 2012). DHEAS is transported by OATP1A2, OATP1B1, OATP1B3, and OATP2B1 (Kullak-Ublick et al., 1998, 2001; Cui et al., 2001; Pizzagalli et al., 2003; Grube et al., 2006a; Yang et al., 2011). Under conditions of androgen depletion, the expression of OATP1A2 significantly increases, and in OATP1A2 knockdown cells DHEAS does not stimulate cell growth, suggesting that OATP1A2 is important for DHEAS-mediated growth of prostate cancer cells (Arakawa et al., 2012). In contrast, two docetaxel-resistant patient-derived xenografts were found to have marked decrease in *SLCO1B3* expression, which reduced the uptake of docetaxel into these cells (de Morrée et al., 2016). Thus, up- and downregulation of OATP transporters in prostate cancer cells may have varying effects depending on whether a cytotoxic agent or tumor growth-promoting endogenous substrate is being transported.

Due to their role in steroid transport, OATPs may impact prostate cancer prognosis. In one study, carriers of the reference SNP (rs) 12422149 in *SLCO1B1* or the rs4149117 in *SLCO1B3* had a higher rate of prostate cancer-specific mortality compared with wild type (Wright et al., 2011). In men with prostate cancer, those with at least one copy of the *SLCO1B3* c.334T>G variant have been shown to have longer time to response to androgen deprivation therapy (Sharifi et al., 2008) and a trend toward shorter time to progression to castration-resistant prostate cancer (Fujimoto et al., 2013) compared with wild type, likely due to increased transport of testosterone into the tumor by the T allele (Sharifi et al., 2008). In another study, patients with the *SLCO1B3* c.334GG/699AA haplotype had longer median survival (8.5 vs. 6.4 years) and improved survival to 10 years (42% vs. 23%) compared with patients with TT/AA or TG/GA haplotypes (Hamada et al., 2008). This evidence suggests that *SLCO1B3* variation may aid in prognostication for prostate cancer.

The *SLCO2B1* variant c.935G>A has been shown to affect DHEAS uptake, with the variant transporter having less

DHEAS transport compared with wild type; accordingly, a cell growth assay showed that the wild-type transporter was associated with increased cell proliferation (Yang et al., 2011). Patients with prostate cancer with at least one copy of the variant allele at rs12422149 in *SLCO2B1* have longer time to progression on antiandrogen therapy, suggesting an improved prognosis conferred by the variant genotype, likely due to reduced transport of DHEAS into the tumor by the variant allele (Yang et al., 2011; Fujimoto et al., 2013). Two other *SLCO2B1* variants (rs1077858 and rs1789693) also affect time to progression in prostate cancer, with the variant alleles being associated with longer time to progression. Patients with more than one risk genotype in *SLCO2B1*, or with an at-risk genotype in both *SLCO1B3* (which did not reach significance on their own) and *SLCO2B1*, had progressively worse outcomes as the number of at-risk genotypes increased (Yang et al., 2011).

Hepatic Tumors. OATP1B1 and OATP1B3, while highly expressed in normal liver tissues, are generally downregulated in hepatic tumors to varying degrees in different studies (Kinoshita and Miyata, 2002; Cui et al., 2003; Vavricka et al., 2004; Zollner et al., 2005; Libra et al., 2006; Pressler et al., 2011; Wlcek et al., 2011; Vasuri et al., 2011; Buxhofer-Ausch et al., 2013). In one study, 45% of hepatocellular carcinoma specimens lacked staining for both OATP1B1 and OATP1B3 (Vasuri et al., 2011). In addition, the pattern of OATP1B3 staining is different in malignant cells (cytoplasmic) versus normal tissue (membranous) (Libra et al., 2006), and progressive loss of OATP1B3 staining is seen as tumor grade increases, suggesting that the lowest OATP1B3 expression is associated with the most aggressive tumors (Lockhart et al., 2008). Neither OATP1B1 nor OATP1B3 expression was found in lymph node metastases of hepatocellular carcinoma or in liver metastases from adenocarcinoma of the colon, rectum, or pancreas, and normal liver tissue surrounding these metastatic lesions maintained normal OATP1B1 and OATP1B3 expression (Cui et al., 2003). OATP2B1 mRNA levels were found to be lower in malignant versus normal cells in some studies (Pressler et al., 2011; Wlcek et al., 2011), but in another study OATP2B1 mRNA expression was similar or higher in malignant versus normal hepatic cells (Libra et al., 2006). Other OATPs are also overexpressed in malignant versus normal hepatic tissue (Wlcek et al., 2011).

The conjugation of drugs to bile acids has been studied as a way to selectively deliver these drugs, including chemotherapy agents, to the liver (Kramer et al., 1992). There is evidence that uptake of bile acid derivatives into human hepatic cancer cells is OATP mediated (Kullak-Ublick et al., 1996, 1997). An imaging agent that is a bile acid derivative is transported by OATP1B3, which is significantly underexpressed in liver tumors compared with normal liver; therefore, the use of this agent could allow for improved visualization of liver tumors (Libra et al., 2006). Decreased protein expression of these OATP transporters in malignant tissues may be important given the role of these transporters in the uptake of chemotherapy agents, with reduced expression leading to decreased tumoral uptake of these drugs.

Colorectal and Other Gastrointestinal Tumors. OATP1A2 mRNA has been detected in colon adenocarcinoma specimens (Tamai et al., 2000), but was found to be expressed at lower levels in colon neoplasia specimens compared with normal colon, which has implications for the

use of chemotherapy agents transported by OATP1A2 in the management of gastrointestinal cancers (Ballestero et al., 2006). OATP1B1 and OATP1B3 mRNA are highly expressed in various cancers of the gastrointestinal tract including the colon, despite not being found in normal colon tissue (Abe et al., 2001; Ballestero et al., 2006; Buxhofer-Ausch et al., 2013), with higher OATP1B1 expression associated with higher tumor grade in colon cancer specimens (Pressler et al., 2011). OATP1B3 has been detected in gastric and gallbladder cancers (Abe et al., 2001; Lancaster et al., 2013). In one study, out of 30 colorectal cancer specimens studied, 27 were positive for OATP1B3 by immunohistochemistry, with the remaining three specimens expressing a mutant form of OATP1B3 that caused the antibody binding for the immunohistochemical staining to fail; the OATP1B3 staining in these samples was primarily cytoplasmic, in contrast to the membranous pattern found in normal liver (Evangeli et al., 2017). Another study similarly found that while none of the normal colon specimens had OATP1B3 mRNA present, four out of the seven colon cancer specimens studied had detectable OATP1B3 mRNA that was almost exclusively a cancer-specific isoform different from that found in normal liver (Nagai et al., 2012).

Overexpression of OATP1B3 mRNA in a colorectal cancer cell line was associated with reduced drug-induced apoptosis of these cells and reduced transcriptional activity of the tumor suppressor p53; these functions are apparently directly related to OATP1B3-mediated transport, since inclusion of a point mutation that abolishes OATP1B3 transport also removed the antiapoptosis and reduced p53 features of these cells (Lee et al., 2008). OATP2B1 mRNA has been detected in colon adenocarcinoma samples (Tamai et al., 2000; Bleasby et al., 2006; Kleberg et al., 2012) with higher expression in neoplastic colon specimens compared with normal colon (Kleberg et al., 2012).

Pancreatic Tumors. OATP1B3 is expressed in pancreatic cancer samples at higher levels than in normal pancreas (Abe et al., 2001; Kounnis et al., 2011, 2015; Buxhofer-Ausch et al., 2013; Hays et al., 2013; Lancaster et al., 2013). OATP1A2 (Kounnis et al., 2011) and OATP1B1 (Kounnis et al., 2011, 2015) are also highly expressed in pancreatic tumors. OATP1B3 expression was found to be highest in the non-malignant conditions of pancreatic hyperplasia and pancreatitis, and was also high in stage 1 pancreatic adenocarcinoma, with lower levels of expression seen in stage 2 or 3 adenocarcinoma, suggesting that OATP1B3 expression could be useful as a marker to detect premalignant lesions or early stage pancreatic cancer (Hays et al., 2013).

Lung Tumors. OATP1A2 (Brenner et al., 2015) and OATP2B1 (Bleasby et al., 2006; Brenner et al., 2015) mRNA are expressed at low levels in normal lung epithelium. OATP1A2 mRNA was found at similar (Monks et al., 2007) or lower (Brenner et al., 2015) levels in malignant lung tissue compared with normal tissue, while OATP2B1 mRNA was found to be upregulated in malignant lung tissue compared with normal in one study (Brenner et al., 2015) and downregulated in malignant tissue in another study (Monks et al., 2007). Minor OATP2B1 mRNA expression in lung tumor specimens was detected in another study, although quantification compared with normal tissue was not done (Bleasby et al., 2006). OATP1B1 and OATP1B3 have also been shown to be expressed in some lung tumor specimens (Buxhofer-Ausch et al., 2013), and *SLCO1B3* mRNA was found in malignant

lung cells (Lancaster et al., 2013). No mRNA expression of OATP1B3 was found in normal lung tissues, while the cancer-specific OATP1B3 was found in two out of five lung cancer specimens studied (Nagai et al., 2012).

Conclusions

Over the past two decades, OATPs have increasingly become recognized as important mediators of drug uptake and disposition. More recently, it has become apparent that OATPs have potentially important emerging roles in cancer pharmacology. Transport of many chemotherapy agents is mediated by OATPs, which may have significant implications for chemotherapy disposition and drug-drug interactions. OATPs are polymorphic with numerous function-altering variants that can alter the disposition, efficacy, and toxicity profiles of chemotherapy agents; this is especially notable for drugs that traditionally have narrow therapeutic indices and has important implications for personalized and precision medicine initiatives. OATPs are widely and differentially expressed in several normal and neoplastic tissues and transport many substrates that are of importance in cancer therapy and tumor progression. Transport of endogenous steroid hormones is associated with cell proliferation in some hormone-dependent cancers, and overexpression of OATPs in these tumors may lead to more aggressive disease. Differential expression of OATPs in neoplastic tissues may provide novel therapeutic strategies to preferentially deliver chemotherapy to tumor tissues with OATP overexpression to enhance tumor killing while minimizing damage to normal tissues.

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