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Contribution of Tumoral and Host Solute Carriers to Clinical Drug Response

Jason A Sprowl¹, Torben S Mikkelsen², Hugh Giovino^{1,3}, and Alex Sparreboom^{1,*}

¹Department of Pharmaceutical Sciences, St. Jude Children's Research Hospital, Memphis, Tennessee, USA

²Department of Pediatric Oncology, Skejby Hospital, Aarhus University Hospital, Denmark

Abstract

Members of the solute carrier family of transporters are responsible for the cellular uptake of a broad range of endogenous compounds and xenobiotics in multiple tissues. Several of these solute carriers are known to be expressed in cancer cells or cancer cell lines, and decreased cellular uptake of drugs potentially contributes to the development of resistance. As result, the expression levels of these proteins in humans have important consequences for an individual's susceptibility to certain drug-induced side effects, interactions, and treatment efficacy. In this review article, we provide an update of this rapidly emerging field, with specific emphasis on the direct contribution of solute carriers to anticancer drug uptake in tumors, the role of these carriers in regulation of anticancer drug disposition, and recent advances in attempts to evaluate these proteins as therapeutic targets.

Keywords

Anticancer drugs; Drug disposition; Pharmacodynamics; Solute carriers

1. INTRODUCTION

Membrane-localized transport proteins have evolved to catalyze migration or expulsion of an endogenous or exogenous molecule across biological membranes. Such evolution has been necessary because membrane lipid bilayers would otherwise present virtually impenetrable barriers to many molecules or, alternatively, permit excessive intracellular accumulation. Hence, it became possible to regulate the composition of intracellular and extracellular fluids with the advent of membrane transport proteins ("transporters") (Van Winkle, 1999). Contemporary bioinformatics analyses have provided an emerging picture of how the majority of membrane transporters probably evolved, and such studies have allowed postulation of the specific pathways taken for their appearance (Saier, 2003).

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*Address correspondence to this author at St. Jude Children's Research Hospital, 262 Danny Thomas Place, Memphis, TN 38105, CCC, Room I5308. Phone: (901) 595-5346; Fax: (901) 595-3125; alex.sparreboom@stjude.org.

³Current address: Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, North Carolina, USA.

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Until recently, the number of identified membrane transporters in mammalian species was relatively modest, but in the post-genomic era this number is now rapidly increasing; based on homology/motif searching and semi-automated curation, the TransportDB web site currently lists as many as 1022 transporters for *Homo sapiens* alone (<http://www.membranetransport.org/> Accessed: August 2011). Although most of these transporters have unknown physiologic function, several have gained interest within the scientific community at an ever increasing rate, which is due, in part, to the recognition that drugs may ‘hitchhike’ on these proteins that normally act on endogenous substrates. While the concept of a transporter-mediated movement of certain drugs in and out of cells was already proposed in the 1950s (Lotspeich, 1958), it was not until the first solute carriers were cloned in the 1990s that this field truly flourished (Grundemann et al., 1994; Jacquemin et al., 1994; Sekine et al., 1997; Sweet et al., 1997). Since then, the physiological and pharmacological role of several transporter proteins has been studied in a wide range of therapeutic disciplines, including oncology, cardiovascular diseases, infectious diseases, and diabetes.

The solute carriers comprise of over 300 proteins organized into 51 distinct families (<http://www.bioparadigms.org/slc/menu.asp>) that do not require ATP in order to function and are commonly classified as passive transporters, ion coupled transporters, or exchangers (Hagenbuch, 2010; Hediger et al., 2004). Perhaps the largest contributing factor to the apparent historic lack of interest in solute carrier research is the long-held belief that most xenobiotics are transported across membranes via passive diffusion at a rate related to their hydrophobicity (Dobson and Kell, 2008). Instead, evidence accumulated over the last decade now supports the notion that solute carrier-mediated migration of drugs across the highly organized lipid bilayers of biological membranes is an important mechanism of cellular uptake, especially of low-permeable agents (Van Winkle, 1999).

One line of evidence supporting the importance of solute carrier mediated cellular uptake of anticancer drugs is that there are now many cases in which drugs are known to be taken up into cells via defined transporters (Table 1). Another line of evidence is the notion that there are anticancer drugs which specifically accumulate in particular organs causing tissue-specific toxicity and that this process can be altered by chemical inhibitors of solute carriers (Zolk and Fromm, 2011). Furthermore, several solute carriers are known to be expressed in cancer cells or cancer cell lines (Huang et al., 2004; Okabe et al., 2008), and decreased cellular uptake of drugs into cancer cells is known to potentially contribute to the development of resistance to various agents, including platinum-based chemotherapeutics (Hall et al., 2008; Helleman et al., 2006; Liang et al., 2004; Shen et al., 2000). As a result, the expression levels of these proteins in humans have important consequences for an individual’s susceptibility to certain drug-induced side effects, interactions, and treatment efficacy. Additionally, interindividual variation in the pharmacokinetic profiles of anticancer drugs often leads to variability in the pharmacodynamic effects of a given dose of a drug. That is, an identical dose of drug may result in acceptable toxicity in one patient, and unacceptable and possibly life-threatening toxicity in another; or clinical response in one individual and drug resistance leading to cancer progression in another. Since solute carrier function in organs of absorption (gut) and elimination (kidney, liver) have the potential to modulate pharmacokinetic profiles of multiple anticancer drugs, these transporters can indirectly modulate tumoral drug levels. This concept has not been reviewed as extensively as the ABC family of transporters, with the exception of a few recent reports (Anderson and Thwaites, 2010; Dobson et al., 2009; Giacomini et al., 2010; Nies et al., 2011). In our review, we discuss the contribution of solute carriers to anticancer drug response or pharmacokinetics in humans. Rather than being exhaustive, we attempted to illustrate the key principles that have resulted in advancements of this field, such as relationships between

pharmacokinetic parameters and antitumor efficacy on the basis of a select example of compounds.

2. TAXANES

2.1. Tumoral Solute Carriers and Taxane Uptake

The taxanes paclitaxel and docetaxel, tubulin-interactive agents, are among the most widely used chemotherapeutic agents and have been approved for the treatment of breast, lung, ovarian, prostate, and gastric cancers. Paclitaxel and docetaxel are high-affinity substrates of the organic anion transporting polypeptides OATP1B1 (formerly OATP2, OATP-C, LST-1; gene, *SLCO1B1*, *SLC21A6*) and OATP1B3 (OATP8, LST-2; gene, *SLCO1B3*, *SLC21A8*). These transporters are expressed exclusively in the liver and are localized to the basolateral (or sinusoidal) membrane of hepatocytes. Interestingly, OATP1B3 and to a lesser extent OATP1B1 are abundantly expressed in cancer cell lines and human tumors, including hepatocellular (Cui et al., 2003; Kinoshita and Miyata, 2002; Vavricka et al., 2004; Zollner et al., 2005), colorectal (Lockhart et al., 2008), ovarian (Svoboda et al., 2011), and prostate cancers (Hamada et al., 2008). It is tempting to speculate that OATP1B1 and OATP1B3 may play a role in determining cellular sensitivity to anticancer substrate drugs. Indeed, preclinical *in vitro* studies have suggested that low expression of these transporters in the human hepatoma cell line HepG2 and the ovarian cancer cell line SKOV-3 is associated with reduced influx of paclitaxel and decreased cytotoxicity (Svoboda et al., 2011). However, to our knowledge, such associations have not yet been reported in cancer patients treated with taxane-containing antineoplastic regimens, and therefore the clinical significance of these findings remains unclear.

2.2. Indirect Contribution of Host Carriers to Taxane Efficacy

The pharmacokinetic profile of paclitaxel and docetaxel is characterized by substantial interindividual variability, with up to 10-fold differences in drug clearance even in patients with normal hepatic function (Baker et al., 2006). This degree of variability has important toxicological and therapeutic ramifications, as measures of systemic exposure to paclitaxel and docetaxel are known predictors of time to tumor progression in patients with non-small cell lung cancer (Baker et al., 2006).

A critical determinant of the interindividual pharmacokinetic variability for taxanes is associated with differential expression of polymorphic drug-metabolizing enzymes and/or transporters at sites of elimination, in particular the liver. There is compelling evidence that the initial entry of the taxanes into hepatocytes from sinusoidal blood is regulated, at least in part, by OATP1B1 and OATP1B3 (Baker et al., 2009; Smith et al., 2005; Svoboda et al., 2011; Takano et al., 2009; Yamaguchi et al., 2008). This supposition is consistent with recent findings from a study performed in mice that are deficient in the single murine OATP1B subfamily member, Oatp1b2 (*Slco1b2*, formerly *mlst-1*, *mOatp4*, *Slc21a10*) (van de Steeg et al., 2011). This investigation revealed that the systemic exposure to paclitaxel, when administered at a dose of 10 mg/kg was increased by more than 2-fold in Oatp1b2-deficient mice compared with wildtype animals, whereas the liver uptake of paclitaxel was reduced by about 2-fold (van de Steeg et al., 2011). These findings are consistent with several exploratory pharmacogenetic-association studies indicating that certain variant alleles in the *SLCO1B3* gene (rs11045585) are associated with an increased incidence of docetaxel-induced toxicity (Kiyotani et al., 2008) and lower clearance (Chew et al., 2011) in Asian patient populations. Similar investigations performed in cohorts of patients of European ancestry, focusing specifically on common nonsynonymous polymorphisms in *SLCO1B3* (Schwarz et al., 2011), have failed so far to identify statistically significant

genetic predictors of paclitaxel (Smith et al., 2007) or docetaxel clearance (Baker et al., 2009) and therefore, further study is required in order to confirm any clinical significance.

With docetaxel given as a short intravenous infusion, the main dose-limiting toxicity associated with treatment, neutropenia, occurs in virtually all patients given a dose between 60–100 mg/m², and severe neutropenia occurs in up to 85% of patients given 100 mg/m² or in up to 75% of patients given 60 mg/m². Curiously, the incidence of severe neutropenia is substantially reduced in castrated patients with prostate cancer compared with non-castrated patients with prostate cancer or patients with other solid tumors, despite the similarity in total dose administered per course (Sparreboom, 2011). A recent study suggests that this decreased incidence of neutropenia in castrated patients is associated with an increased hepatic uptake of docetaxel, leading to a decrease in systemic exposure (Franke et al., 2010a). This phenomenon, in turn, is linked with an increase in the hepatocellular expression of the docetaxel transporter SLC22A7 (OAT2) after castration (Franke et al., 2010a). This suggests that castrated patients with prostate cancer undergoing docetaxel treatment should be capable of tolerating elevated doses to offset their intrinsically increased ability to clear the drug. Furthermore, the increased clearance of docetaxel found following castration implies that these patients may not be benefiting optimally from standard dosages of docetaxel and may require a dosage increase to prevent undertreatment.

3. IMATINIB

3.1. Tumoral Solute Carriers and Imatinib Uptake

Imatinibmesylate is the first approved rationally designed inhibitor of specific protein tyrosine kinases. The drug inhibits ABL and the BCR-ABL fusion protein [expressed in Philadelphia chromosome–positive chronic myeloid leukemia (CML)], c-KIT [expressed in gastrointestinal stromal tumors (GIST)], and the platelet-derived growth factor receptor (PDGF-R; i.e., expressed in some sarcomas) (Buchdunger et al., 1996; de Jong and Verweij, 2003; Lydon and Druker, 2004). Imatinib has become the standard treatment for patients with chronic myeloid leukemia (Druker et al., 2006; O'Brien et al., 2003) and GIST (Demetri et al., 2002; Joensuu et al., 2002; van Oosterom et al., 2001; Verweij et al., 2004).

Although response rates in imatinib-treated patients are high, ranging between 70 to 90% of patients with GIST as well as CML (Blanke et al., 2008; Druker, 2008; Verweij et al., 2004), nonresponse or disease progression after a certain period of time occurs frequently. Genetic mutations or gene amplification of the drug targets are known mechanisms for this observed resistance phenotype (Heinrich et al., 2006; Liegl et al., 2008), however, accumulating data indicate an important contributing role of specific tumoral transporters in the antitumor activity of imatinib. Emerging evidence suggests that a measure of activity for organic cation transporter 1 (OCT1; SLC22A1) is a critical determinant of therapeutic outcome in patients with CML receiving imatinib therapy (Eechoute et al., 2011b; Engler et al., 2011). Thomas et al. were the first to show that inhibition of OCT1 function in peripheral blood leukocytes from patients with CML was associated with a decreased intracellular uptake of imatinib (Thomas et al., 2004). This finding was confirmed in another study, showing that imatinib uptake in a CML cell line significantly correlated with OCT1 mRNA expression (Wang et al., 2008). Furthermore, White et al. found that *ex vivo* sensitivity for imatinib strongly correlated with the intracellular uptake and retention of imatinib in mononuclear cells of untreated patients with CML (White et al., 2006). When prazosin, an OCT1 inhibitor, was added to these cells, the concentration needed to inhibit molecular drug targets was significantly increased. In addition, it was also shown that only the activity of OCT1 in mature CML blasts is associated with therapeutic outcome and not the OCT1 activity in immature CD34⁺ cells (Engler et al., 2010). This could imply that effective intratumoral accumulation of imatinib may be decisive for therapeutic response in CML. Nonetheless,

pretreatment OCT1 expression levels in patients with CML were 8 times higher in responders than in non-responding patients (Crossman et al., 2005), which was confirmed in another study, where high baseline OCT1 mRNA expression levels correlated with better cytogenetic response at 6 months and prolonged progression-free and overall survival (Wang et al., 2008). White and colleagues also showed that chronic phase CML patients with low OCT1 activity did benefit from imatinib dose escalation, although no correlation between clinical efficacy and OCT1 mRNA levels was reported (White et al., 2007).

Curiously, a number of studies have indicated that imatinib itself is at best a poor transported substrate of OCT1 (Hu et al., 2008; Wang et al., 2008). Considering that prazosin is also not an inhibitor specific to OCT1 (Forchap et al., 2011), it is possible that OCT1 gene expression is a composite surrogate for other, currently unknown variables in regulating sensitivity of CML cells to imatinib. For example, a recent gene expression analysis indicated that OCT1 expression is inversely correlated with the expression of multiple efflux transporters for which imatinib is a known substrate, including ABCB1 and ABCG2 (Hu et al., 2008). As such, OCT1 gene expression could merely be an indirect marker of imatinib transport or cellular accumulation and therefore, the *in vitro* or expression associations requires further study in order to elucidate its clinical relevance.

3.2. Indirect Contribution of Host Carriers to Imatinib Efficacy

In recent years, it has become increasingly appreciated that many molecularly-targeted agents, including imatinib, have a relatively narrow therapeutic window and that this recognition demands that rigorous efforts be made to characterize their pharmacokinetic properties and optimize their therapeutic regimens (Baker and Hu, 2009). Indeed, failure to recognize this early on during drug development may lead to suboptimal dosing strategies, eventually resulting in lack of efficacy. In the case of imatinib, evidence is emerging that drug resistance is directly linked with measures of systemic exposure. For instance, steady-state plasma levels of imatinib in non-responding patients are known to be significantly lower than in responding patients with CML (Larson et al., 2008; Picard et al., 2007; Widmer et al., 2010) or GIST (Demetri et al., 2009). Moreover, imatinib pharmacokinetic parameters may contribute to an acquired drug resistance phenotype, as was suggested in a population pharmacokinetic study in a small cohort of patients with GIST (Judson et al., 2005). In particular, after long-term treatment (>1 year), the apparent oral clearance of imatinib increased by 33%, compared with the start of treatment. This change in pharmacokinetic properties is likely related to the reduced side effects over time, and may also explain why dose escalation of imatinib at first progression results in clinical benefit in subsets of patients with advanced CML or GIST (Kantarjian et al., 2009; Park et al., 2009; Zalcberg et al., 2005).

Previous studies indicate that imatinib is almost completely absorbed and has an oral bioavailability >90% (Peng et al., 2004). This is somewhat unexpected considering the affinity of imatinib for a number of intestinal efflux transporters such as ABCB1 and ABCG2 (Burger et al., 2004; Hamada et al., 2003), and the notion that under the acidic condition in the duodenum, imatinib is predominantly charged (~90% monocationic at pH 5–6) (Szakacs et al., 2005). The cationic properties of imatinib in the acidic milieu of the gastrointestinal tract suggest that passive permeability is impaired and that uptake of imatinib across the intestinal wall may be facilitated by one or more carriers. One possible candidate involved in this process is SLCO1A2 (formerly, OATP-A, OATP1, OATP, OATP1A2) (Hu et al., 2008), which has been reported to be expressed in duodenal enterocytes (Glaeser et al., 2007), and can transport imatinib in transfected *in vitro* model systems. Although the expression of SLCO1A2 in the small intestine has been a subject of controversy, as reviewed by Tamai (Tamai, 2011), recent studies indicate that certain promoter polymorphisms in the SLCO1A2 gene might be associated with the

pharmacokinetics of imatinib in patients with CML (Yamakawa et al., 2011). Unfortunately, this association has not been observed for multiple common non-synonymous variants (Eechoute et al., 2011a). Additional studies reported to date that have assessed the possible role of genetic polymorphisms in solute carriers with imatinib therapy have been limited to OCT1 and OATP1B3, and have resulted in inconsistent, conflicting information (Hu et al., 2008; Kim et al., 2009; Takahashi et al., 2010; Zach et al., 2008).

4. PLATINUMS

4.1. Tumoral Solute Carriers and Platinum Uptake

Platinum-based chemotherapeutics are also among the most widely used antineoplastic agents for the treatment of various human malignancies including lung, bladder, ovarian, testicular, head and neck and colon cancer (Chitapanarux et al., 2010; Collins et al., 2011; Goldberg et al., 2004; Horn et al., 2011; Nichols and Kollmannsberger, 2011; Shelley et al., 2011). Cisplatin, the original platinum-based compound used for chemotherapy, was approved for clinical use in 1978 (Higby et al., 1974). Even today, cisplatin remains the most widely used agent in the United States (McWhinney et al., 2009). It is believed to act by cross-linking interstrand or intrastrand nuclear DNA, which initiates DNA damage response signaling, resulting in cell cycle arrest and apoptosis (Siddik, 2003; Zwelling and Kohn, 1979). While cisplatin is quite effective, especially in the treatment of testicular cancer, with 90–95% survival rates (Raghavan, 2003), its use is greatly limited to the onset of nephrotoxicity, neurotoxicity, gastrointestinal toxicity and ototoxicity (McWhinney et al., 2009). Therefore, investigations involving additional platinum-based compounds have identified new platinum drugs with decreased toxicity.

Carboplatin was approved in 1989 and although it is currently used in first line combination treatment for ovarian and lung cancer, its effectiveness is commonly lower than cisplatin when used to treat other malignancies and is commonly cross-resistant with cisplatin (Ardizzoni et al., 2007; Schuler et al., 2010). The use of carboplatin is also limited by the onset of thrombocytopenia and higher risk of anemia although patients experience lower incidences of neurotoxicity, nausea, hearing loss or renal toxicity than patients treated with cisplatin (Ardizzoni et al., 2007; McWhinney et al., 2009; Rajeswaran et al., 2008). A third generation platinum compound, oxaliplatin, was the latest platinum agent to be FDA approved (Ibrahim et al., 2004). Oxaliplatin differs from cisplatin and carboplatin in that it has been shown to be effective in treatment of metastatic colorectal cancer, a malignancy commonly resistant to platinum chemotherapeutics, and retains its antineoplastic properties in certain cisplatin and carboplatin resistant tumors (Mishima et al., 2002; Raymond et al., 2002; Rixe et al., 1996). In addition, oxaliplatin has shown little to no nephro- or ototoxic effects and is less myelosuppressive than carboplatin; however, administration of oxaliplatin is limited by the onset of sensory and motor neuropathy (Ibrahim et al., 2004).

The effectiveness of platinum-based chemotherapy is directly linked with accumulation into the target cell where DNA damage can then occur. Originally, movement of these agents across the cellular lipid bilayer membrane was thought to occur predominantly by passive diffusion (Binks and Dobrota, 1990; Gale et al., 1973). Instead, emerging evidence in the literature indicates that carrier mediated uptake is likely the major determinant of uptake into the cell (Dobson et al., 2009). In fact, the movement of platinum compounds across the lipid bilayer membrane is greatly influenced by multiple families of solute carriers, including copper transporters (CTRs) and the organic cation transporters (OCTs).

Copper transporter proteins are important regulators in maintaining the delicate balance of Cu^+ homeostasis and are members of the SLC31 family of solute carriers. CTR1 (SLC31A1), is made of three transmembrane domains that as a homotrimer with nine

helices form a pore that passes through the lipid bilayer (Nose et al., 2006). Transport of substrates by CTR1 is energy independent, influenced by temperature, pH and the K⁺ gradient (Lee et al., 2002). The physiological importance of CTR1 has been shown by the embryonic lethality of CTR1 knockout in mice and that CTR1 is ubiquitously expressed in all vertebrate tissues (Lee et al., 2001; Zhou and Gitschier, 1997). The potential of CTRs to modulate platinum accumulation has undergone vigorous investigation. CTR1 was initially identified as a mediator of cisplatin cytotoxicity when reduced sensitivity and accumulation of cisplatin was discovered in yeast cells deficient of CTR1 (Ishida et al., 2002). Upon additional experimentation using isogenic CTR1-deficient mouse embryonic fibroblasts, mammalian CTR1 was shown to be involved in the import of cisplatin, carboplatin and oxaliplatin (Larson et al., 2009). Additionally, the related solute carrier CTR2 (SLC31A2) has also been shown to have a role in the accumulation and the cytotoxic properties of cisplatin and carboplatin (Blair et al., 2009). Due to their role in maintaining Cu⁺ homeostasis, intracellular copper can downregulate CTR1 levels in order to prevent Cu⁺ toxicity (Petrus et al., 2003). Therefore, it is not surprising that cisplatin was shown to result in rapid degradation of CTR1 by endocytosis and macropinocytosis (Holzer and Howell, 2006; Holzer et al., 2006; Jandial et al., 2009). These studies also used the proteasome inhibitors bortezomib and bortezomib which prevented down-regulation of CTR1 and was synergistic in promoting tumor cell death. In fact these studies appear to explain the success of phase I and phase II clinical trials assessing the efficacy of the combination of bortezomib with carboplatin (Aghajanian et al., 2005; Davies et al., 2009).

Although the importance of CTRs has been well documented *in vitro*, the relevance of these transporters *in vivo* has yet to be established. Furthermore, the association of resistance of cancer cells to cisplatin with expression of CTR1 has only been shown in very few cell lines (Beretta et al., 2004; Matsumoto et al., 2007a; Noordhuis et al., 2008; Zisowsky et al., 2007). These findings may possibly be explained by previous investigations that identified some platinum resistant cells are unable to glycosylate CTR1 at Thr27, resulting in protease-dependent removal of the N-terminus, rendering the protein inactive while the remaining structure of the protein is left intact (Maryon et al., 2009). However, again whether this possibility is of clinical relevance remains to be seen.

Recently an additional class of solute carrier transporters, the SLC22 family of organic cation transporters, has been implicated in the uptake of platinum chemotherapeutics. The solute carrier OCT2 (or SLC22A2) has been shown by various investigators to efficiently transport cisplatin and oxaliplatin, but not carboplatin (Burger et al., 2010; Filipinski et al., 2008; Zhang et al., 2006). Currently, no clinical data exists suggesting that OCT2 is a critical determinant of cisplatin uptake or resistance in cancer cells. An investigation of the NCI60 panel of cell lines revealed that OCT2 was most highly expressed in ovarian cancer cell lines, suggesting that the efficacy of platinum-based therapy in this disease could possibly be associated with tumoral expression of OCT2. However, in tumor samples obtained from patients with ovarian cancer, expression of OCT2 was found to be either low or absent, and no correlation of expression and outcome was detected (Burger et al., 2010). Interestingly, the ability of OCT2 to transport oxaliplatin is greater than that of cisplatin (Burger et al., 2010; Zhang et al., 2006). Due to high efficiency of oxaliplatin transport, it has been hypothesized that the efficacy of oxaliplatin in the treatment of metastatic colorectal cancer may be a result of high OCT2 expression in colon cancer specimens, while it appears absent in normal colon samples (Zhang et al., 2006). Unfortunately, these results have yet to be repeated in a larger patient population and many colon cancer cell lines appear to lack expression of OCT2 (Burger et al., 2010; Zhang et al., 2006). Therefore, it is unlikely that OCT2 expression or function will predict the efficacy of platinum-based treatment.

4.2. Indirect Contribution of Host Carriers to Platinum Efficacy

As mentioned previously, the OCTs are a subgroup of the SLC22A family that includes SLC22A1 (OCT1), SLC22A2 (OCT2) and SLC22A3 (OCT3). These transporters are characterized by their 12 transmembrane domains and a broad range of substrates which include neurotransmitters, hormones and various xenobiotics that are positively charged (Ciarimboli, 2008). Furthermore, these carriers function bi-directionally, as well as pH- and Na⁺-independently, although, their function is voltage dependent. Tissue distribution of these transporters is species dependent but their main function is the movement of organic cations across the membrane, more specifically moving these molecules from the basal membrane into the cell. Early indications that SLC22A family members were involved in platinum organ accumulation were made when it was determined that OCT expression was high in tissues that were frequently targets of toxicity by platinum drugs and that administration of cisplatin could inhibit uptake of tetraethyl ammonium (TEA) in rat kidneys (Nelson et al., 1984). Given that cisplatin is mainly eliminated via urinary excretion, expression or function of OCTs can potentially alter systemic levels of platinum compounds and therefore indirectly regulate the concentration of platinum that reaches tumor cells. As a result, since the discovery of SLC-dependent uptake of platinum, each SLC22A family member has been observed individually for their ability to transport platinum drugs.

The first identified member of the organic cation transporters was OCT1 which was isolated and cloned from rats (Grundemann et al., 1994). Human OCT1 is predominantly expressed and localized at the basolateral or sinusoidal membrane where it regulates uptake of organic cations into hepatocytes (Gorboulev et al., 1997). Cisplatin was previously identified as a substrate for human OCT1, as was the platinum-derivative picoplatin (More et al., 2010b; Yonezawa et al., 2006; Zhang et al., 2006). However, in contrast to these studies some have demonstrated that overexpression of rat or human OCT1 did not increase cisplatin accumulation or that cisplatin was unable to inhibit cellular uptake of the fluorescent compound cation 4-[4-(diethylamino)styryl]-N-methylpyridiniumiodide (ASP⁺) (Briz et al., 2002; Ciarimboli et al., 2005; Yonezawa et al., 2005). Interestingly, while expression of OCT1 appears to be mainly localized to hepatocytes in humans, murine expression of OCT1 has been detected in both hepatocytes and the kidney (Gorboulev et al., 1997). In fact, OCT1 alone does appear to have an important role in cisplatin pharmacokinetics *in vivo* (Filipski et al., 2009). Urinary elimination of cisplatin was greatly reduced in mice deficient of both OCT1 and OCT2, although, the plasma concentrations of cisplatin were unchanged in these animals. These results suggest that additional studies are required to determine whether tumor efficacy or platinum-induced toxicities could be altered when endogenous OCT1 and OCT2 function is lost in humans.

Much like the controversy of cisplatin transport by OCT1, conflicting studies exist in regards to OCT1 transport of oxaliplatin. Studies performed *in vitro* have identified oxaliplatin as a substrate of OCT1, although administration of oxaliplatin to OCT1-deficient mice does not result in differential plasma pharmacokinetic profiles (Li et al., 2011; Zhang et al., 2006). Meanwhile, although literature is scarce, carboplatin appears to be either a weak substrate for OCT1, or may not be a substrate at all (Yonezawa et al., 2006; Zhang et al., 2006).

The expression of OCT2 has been predominantly located on the basolateral membrane of all three segments of the proximal tubules in human kidneys (Motohashi et al., 2002). Considering that OCT2 is the dominant organic cation transporter located in the proximal tubules of human kidneys and that cisplatin is known to accumulate in this region and initiate nephrotoxicity, the role of OCT2-dependent platinum uptake has been extensively studied. In support of the hypothesis that OCT2 contributes to cisplatin-induced nephrotoxicity, carboplatin which is non-nephrotoxic, has consistently been shown to not be

a substrate of OCT2 (Ciarimboli et al., 2005; Yokoo et al., 2007; Yonezawa et al., 2006). Furthermore, OCT2 expression has been reported to be higher in males, correlating with the observation in rats that urinary clearance of cisplatin and onset of nephrotoxicity is greater in males than in female (Yonezawa et al., 2005). The first direct evidence that cisplatin was a substrate of OCT2 was shown when cisplatin could compete for TEA uptake in rat OCT2 overexpressing NIH3T3 cells (Pan et al., 1999). Since this discovery many studies have confirmed this finding (Ciarimboli et al., 2005; Filipinski et al., 2008; Tanihara et al., 2009; Yokoo et al., 2007; Yonezawa et al., 2006), while some studies have reported that cisplatin is either a moderate OCT2 substrate or is not transported by OCT2 and does not alter platinum sensitivity (Briz et al., 2002; Burger et al., 2010; Zhang et al., 2006). Although conflicting *in vitro* data exists, substantial *in vivo* evidence has revealed that OCT2 does in fact affect cisplatin pharmacokinetics. Mice deficient in both OCT1 and OCT2 were found to be protected from cisplatin-induced nephrotoxicity and elimination of cisplatin through the urine was only 45% of the administered dose while 91% of the administered dose was ultimately eliminated in the urine of wild-type littermates (Filipinski et al., 2009; Franke et al., 2010b). In support of the role of OCT2 in the transport of cisplatin, Oct1/Oct2 deficient mice were also revealed to be protected from cisplatin-induced ototoxicity (Ciarimboli et al., 2010). Taken together, evidence indicates that OCT2 is likely a major contributor to cisplatin-induced nephrotoxicity, ototoxicity and cisplatin pharmacokinetics (Figure 1).

The majority of recent investigations have indicated that oxaliplatin is an excellent substrate of OCT2, with even higher transport efficiency compared with cisplatin (Burger et al., 2010; Lovejoy et al., 2008; Yokoo et al., 2007; Yonezawa et al., 2006; Zhang et al., 2006), although at least one previous study reported that oxaliplatin is not a substrate (Ciarimboli et al., 2005). Interestingly, while oxaliplatin is considered a better OCT2 substrate, this compound does not induce nephrotoxic effects similar to cisplatin (Raymond et al., 1998). It has been speculated that this paradoxical finding can be explained by the existence of transporters localized to the apical (luminal) membrane of kidney cells that are capable of efficiently secreting oxaliplatin into urine. Two reports indicate that SLC47A1 or SLC47A2 may be the main candidates in removal of oxaliplatin from the proximal tubules (Chen et al., 2009; Yokoo et al., 2007; Yonezawa et al., 2006). SLC47A1 or SLC47A2 belong to the multidrug and toxin extrusion (MATE) family and are also known as MATE1 and MATE2-K, respectively. MATE1 expression has been detected in the liver, kidney and skeletal muscles while MATE2-K expression has so far only been detected in the apical membrane of the proximal and distal convoluted tubules of the kidney (Masuda et al., 2006; Otsuka et al., 2005; Terada and Inui, 2008). Both MATE1 and MATE2-K function by H⁺/organic cation antiport and therefore transport is dependent on the H⁺ gradient (Masuda et al., 2006; Takano et al., 1984; Tsuda et al., 2009). Studies performed assessing cisplatin as a substrate of MATE1 have resulted in conflicting data, although the deletion of MATE1 in mice was shown to slightly increase cisplatin-induced nephrotoxicity (Nakamura et al., 2010; Yokoo et al., 2007; Yonezawa et al., 2006). It is well agreed, however, that human MATE2-K is not an efficient cisplatin transporter (Yokoo et al., 2007; Yonezawa et al., 2006). However, additional *in vivo* work is required to confirm the role of the SLC47A family members in transport of platinum agents from the kidney and tumor cells.

Previous studies have revealed that cisplatin and carboplatin are not substrates of OCT3, which is expressed in the liver, placenta, kidney, heart, lung, brain, intestine and skeletal muscle, although oxaliplatin may be a moderate substrate (Yokoo et al., 2007; Yonezawa et al., 2006; Zhang et al., 2006). However, although an OCT3 knockout mouse model exists, there are currently no reports of alterations in platinum pharmacokinetics.

Two additional SLC22 family members have also been hypothesized to contribute to the pharmacokinetics of platinum chemotherapeutics, namely SLC22A4 (OCTN1) and

SLC22A5 (OCTN2). These transporters are localized to the apical membrane of proximal tubules where OCTN2 prevents L-carnitine wasting using Na⁺ symport to drive L-carnitine back into proximal tubule cells (Tamai et al., 1998). Literature regarding platinum as substrates of OCTN1 and OCTN2 is scarce, however, cisplatin is not considered a substrate of either transporter (Lancaster et al., 2010; Yonezawa et al., 2006). Meanwhile, the potential of oxaliplatin to act as an OCTN1 and OCTN2 substrate has mixed results. Oxaliplatin uptake into OCTN1 or OCTN2 overexpressing HEK293 cells did not differ from control cells and furthermore, oxaliplatin was unable to compete for carnitine uptake in OCTN2 overexpressing HEK293 cells (Lancaster et al., 2010; Yonezawa et al., 2006). However, a recent study did demonstrate that oxaliplatin uptake and cytotoxicity may be regulated by OCTN1 and OCTN2 expression (Jong et al., 2011). Unfortunately, in order to assess whether OCTN1 and OCTN2 are clinically important in oxaliplatin pharmacokinetics or accumulation into particular tissues future *in vivo* studies will be required.

5. Methotrexate

5.1. Tumoral Solute Carriers and Methotrexate Uptake

The gene *SLC19A1* encodes the human reduced folate carrier 1 (RFC), a ubiquitously expressed transporter that mediates active cellular uptake of natural folates (Dixon et al., 1994; Goldman, 1971). Inside cells, folinic acid is converted to tetrahydrofolate, which is an essential cofactor in the *de novo* purine synthesis, DNA synthesis, and methylation of proteins and nucleotides (Fox and Stover, 2008). Human cells cannot synthesize folates; hence, all growing cells are dependent on active uptake and mice that are homozygote deficient for *SLC19A1* die as early embryos (Zhao et al., 2001b). Antifolates are analogous to folinic acid and function by inhibition of dihydrofolate reductase (DHFR) and enzymes in the *de novo* purine synthesis pathway (Mishra et al., 2007). Antifolates have been used in cancer treatment since 1948 when aminopterin was first shown to cause temporary remission of disease in children with acute lymphoblastic leukemia (ALL) (Farber and Diamond, 1948). Today, the most widely used antifolate, methotrexate (MTX), is used in the treatment of multiple diseases including ALL, osteosarcomas, lymphomas, head and neck, bladder, and breast cancer (Catto and Hamdy, 2010; Mikkelsen et al., 2011; Mir et al., 2010; Tobias et al., 2010).

The active transport of folate and antifolates was characterized long before the gene *SLC19A1* was cloned and found to be located at chromosome 21q22.3 (Dixon et al., 1994; Williams and Flintoff, 1995; Yang-Feng et al., 1995). Interestingly, children with trisomy 21 (Down's syndrome) have more toxic side effects to MTX compared to other children, suggesting that they have a high cellular uptake of MTX (Buitenkamp et al., 2010; Garre et al., 1987). *SLC19A1* is found in most tissues and the abundant expression in hepatocytes and kidney tubulus signifies that these organs are key regulators in the folate homeostasis (Whetstone et al., 2002). Although carbamazepine is not a substrate for RFC, this drug can decrease the expression of the gene (Halwachs et al., 2011; Halwachs et al., 2009), and use of anticonvulsant drugs such as carbamazepine in children with ALL is known to increase the systemic clearance of MTX and increase the risk of relapse (Relling et al., 2000). The RFC contains 12 transmembrane domains and the substrate-binding pocket is formed by domain 4, 5, 7, 8, 10 and 11 (Hou et al., 2005; Hou et al., 2006). How the protein mediates active uptake of 5-methyltetrahydrofolate, folinic acid, and antifolates (i.e. MTX, pemetrexate and aminopterin) is not yet fully understood (Goldman, 1971; Goldman et al., 1968; Wang et al., 2004). Thiamine phosphates have recently been identified as RFC substrates and it has been suggested that the folate uptake is driven by an intracellular gradient of organic phosphates that efflux through the RFC (Goldman, 1971; Zhao et al., 2002; Zhao et al., 2001a).

Ever since antifolates were first used in the treatment of childhood ALL 60 years ago, MTX has become an integrated part of treatment protocols worldwide (Mikkelsen et al., 2011). Preclinical studies in cells and mice have guided clinical therapy but the optimal dosing schedule is still not found (Goldin et al., 1956; Kamen, 2008; Kamen et al., 2000; Keefe et al., 1982). The primary hypothesis is that an effective exposure of MTX is attained when plasma concentrations are kept above the saturation threshold for RFC, which has a Michaelis-Menten constant (K_m) for MTX in the range of 1 to 5 μM , whereas for folic acid the K_m value is 0.5 to 1 μM (Zhao et al., 2009a). The plasma concentration of folate is 0.02–0.04 μM and therefore it is reasonable to believe that MTX plasma concentrations above 5–10 μM are sufficiently high to saturate RFC. Interestingly, though, it has been difficult to show clinically that low-dose MTX would demonstrate sufficient efficacy compared to higher doses of MTX in the treatment of ALL. A randomized clinical study in childhood ALL showed that intermediate-dose MTX (1 g/m^2) resulted in higher intracellular concentrations of active MTX, and better antileukemic effects compared to low-dose MTX (Masson et al., 1996; Synold et al., 1994). Another study showed that the use of intermediate-dose MTX translated into better event-free survival compared to low-dose MTX (Mahoney et al., 1998), and subsequent clinical trials have supported this finding (Asselin et al., 2011; Matloub et al., 2011). A recent study on children with ALL showed that continuous infusion with high-dose MTX resulted in significantly higher accumulation of intracellular MTX in leukemia cells when compared to a shorter MTX infusion at the same dose (Mikkelsen et al., 2011). This latter study supports the hypothesis that time above a threshold concentration might be better than high plasma MTX peak concentrations, although it still needs to be determined at what level this threshold should be in order to achieve the optimal antileukemic effects of MTX.

Decreased function or expression of RFC can result in resistance to antifolates as first demonstrated in L5178 murine leukemia cells (Fischer, 1962; Gorlick et al., 1996). Similarly, increased expression of *SLC19A1* or additional copy numbers of chromosome 21 is associated with higher MTX accumulation in leukemia cells and better treatment response to MTX (Belkov et al., 1999; Levy et al., 2003). The expression of RFC in leukemia cells differs widely amongst patients with ALL and low expression has been associated with increased risk of relapse in ALL and osteosarcoma (Ge et al., 2007; Patino-Garcia et al., 2009; Sowers et al., 2011). In contrast, additional copies of chromosome 21 are found in 97–100% of all patients with hyperdiploid ALL (>51 chromosomes) and leukemic blasts from these patients have increased expression of RFC (Belkov et al., 1999; Kager, 2009; Paulsson et al., 2010).

Genetic variation in *SLC19A1* has been associated with treatment response in cancer patients but these genetic variants have not yet been used as predictive or prognostic markers in the clinic. The single nucleotide polymorphism (SNP) 80G>A (rs1051266) is found with a high frequency across many ethnicities and is the most studied SNP in *SLC19A1* (Gregers et al., 2010; Laverdiere et al., 2002). The A allele results in a replacement of Arg27 with His27 in the first transmembrane domain of RFC but the functional and clinical impact of this amino acid change is still not clear. One study has demonstrated that when leukemia cells were exposed to MTX *ex vivo* there was no association between 80G>A and sensitivity (de Jonge et al., 2005). However, in another treatment protocol the G allele was significantly associated with higher risk of relapse (Gregers et al., 2010). Interestingly, there was no association between treatment outcome and the RFC 80G>A variant in children with one extra copy of chromosome 21. It is likely that genetic variants in *SLC19A1* will have the highest impact in the treatment protocols that use the highest cumulative dose of MTX. Unfortunately, only few other SNPs have been investigated in clinical studies *but in vitro* experiments have demonstrated that other SNPs do cause functional alterations in RFC (Flintoff et al., 2004).

5.2. Indirect Contribution of Host Carriers to Methotrexate Efficacy

The interindividual variability in MTX pharmacokinetics can partially be explained by genetic variation in membrane transporter proteins with affinity for MTX (Rau et al., 2006; Trevino et al., 2009). MTX is absorbed through active transport mediated by the RFC and the proton-coupled folate transporter *SL46A1* (*PCFT*) located at the apical membrane of enterocytes (Qiu et al., 2006). Additionally, RFC and PCFT both also facilitate the absorption of natural folates at the apical surface of the small intestine and may be responsible for intestinal uptake of MTX (Qiu et al., 2006; Zhao et al., 2008). It was recently discovered that PCFT has a high affinity for 5-methyltetrahydrofolate (K_m 0.8 μM) and that mutations in *SLC46A1* are responsible for hereditary folate malabsorption (Zhao et al., 2009b). Systemic clearance of MTX happens primarily through renal glomerular filtration and active secretion over the proximal tubular cells. Several renal transporter proteins have affinity for MTX, including OAT1, OAT2, RFC, ABCG2, ABCC2, and ABCC4, and polymorphisms in some of these transporters have been associated with MTX clearance (Figure 2) (El-Sheikh et al., 2007; Hulot et al., 2005; Rau et al., 2006; Uwai et al., 2004; van Aubel et al., 2002; VanWert and Sweet, 2008; Vlaming et al., 2009b).

Hepatic uptake of MTX involves the *SLCO* family of genes that encode organic anion transporting polypeptides (OATP). Polymorphisms in several of these genes, including *SLCO1B1* (OATP1B1) and *SLCO1B3* (OATP1B3) have recently been found to explain up to 10% of the interindividual variability in clearance of high-dose MTX (Abe et al., 1999; Abe et al., 2001; Trevino et al., 2009; van de Steeg et al., 2009). The majority of MTX in hepatocytes re-enters the blood circulation by transporter proteins *ABCC3* and *ABCC4*, which are located on the basolateral membrane, although a portion of MTX is excreted into the bile duct, predominantly via *ABCC2* (Kitamura et al., 2008; Vlaming et al., 2006; Vlaming et al., 2008; Vlaming et al., 2009b).

Experiments which to date have studied the pharmacokinetics of MTX in transporter-deficient mice have suggested that Oatp1b2 mediates hepatic uptake of MTX (van de Steeg et al., 2009; Vlaming et al., 2009a; Vlaming et al., 2009b). Although the renal clearance of MTX is known to be higher than the glomerular filtration rate (GFR) in humans and mice, indicating that there must be active tubular secretion of MTX (VanWert and Sweet, 2008), it is less clear how transporter proteins are involved in the renal handling of MTX. The transporter OAT3 (Slc22a8) was thought to be particularly important for the renal clearance for MTX, but only a small difference in MTX clearance has been found between Slc22a8 knock-out mice and wildtype mice (VanWert and Sweet, 2008). Therefore, the indirect influence of transporters of relevance to the pharmacokinetics of MTX on efficacy of treatment requires further study.

6. EXPLOITING SOLUTE CARRIERS AS THERAPEUTIC TARGETS

6.1. Improving the Therapeutic Window of Anticancer Drugs

Considering that organic cation transporters regulate platinum uptake into organs which can modulate their pharmacokinetics and yet appear to play little to no role in tumor uptake, clinical combinations of SLC22 inhibitors may maximize treatment efficacy and decrease toxicity. Theoretically, elimination of the main drug-induced toxicities might allow increased doses of drugs to be administered in order to maximize the therapeutic potential. The SLC22A family members recognize a relatively broad spectrum of substrates and therefore a wide variety of compounds can possibly compete for transport with platinum compounds. The most extensively studied of these compounds is the H₂-receptor antagonist cimetidine, which is commonly prescribed for treatment of heartburn and peptic ulcers by inhibiting production of stomach acid (Burland et al., 1975). Many studies have reported that cimetidine, when administered with cisplatin or oxaliplatin, can inhibit OCT2-

dependent influx (Ciarimboli et al., 2005; Yonezawa et al., 2005). Furthermore, co-administration of cimetidine with cisplatin has been shown to be protective of ototoxicity and partially protective of nephrotoxicity (Ciarimboli et al., 2010; Franke et al., 2010b). Meanwhile, cimetidine was unable to inhibit cisplatin uptake into OCT2-expressing SKOV3 tumor cells, and co-administration of cimetidine with cisplatin did not alter the antitumor efficacy in rats bearing SOSN2 osteosarcomas (Franke et al., 2010b; Katsuda et al., 2010). Therefore, administration of cimetidine with cisplatin may be of great clinical relevance as it appears to decrease cisplatin-dependent toxicities while maintaining tumor efficacy. Unfortunately, it is important to note that cimetidine is an inhibitor of MATE1 and MATE2-K (Meyer zu Schwabedissen et al., 2010; Ohta et al., 2009; Tanihara et al., 2007). These results may indicate that while cimetidine may decrease OCT2-dependent platinum uptake into the cell, MATE1 or MATE2-K efflux may also be compromised, suggesting that a compound that would be selective for OCT2 would be more efficacious. Efforts are currently under way to identify compounds that could be used in conjunction with platinum-based chemotherapy based on a differential ability to inhibit SLC22A- versus SLC47A-family members (Tsuda et al., 2009).

In addition to cimetidine, imatinib also appears to inhibit cellular uptake of cisplatin and decrease nephrotoxicity within rats (Tanihara et al., 2009). As described above, imatinib appears to be a substrate of OCT1 (Minematsu and Giacomini, 2011), however, while this may aid in explaining its protective effects in murine models, OCT2 and not OCT1 is the predominant transporter in human kidneys. Therefore, in order to assess whether the nephroprotective effects of co-administration of imatinib are clinically relevant, additional studies are required.

6.2. Inducing Tumoral Expression to Increase Drug Uptake

A novel therapeutic strategy has recently been proposed based on the premise that a chemical entity which results in enhanced expression of influx transporters in cancer cells would increase the concentration of anticancer substrates within these sites and lead to an increased therapeutic window for chemotherapeutic agents. This concept has been evaluated in neuroblastoma cells, which express the norepinephrine transporter (NET) (More et al., 2011). NET serves as an important uptake protein for the norepinephrine analog, meta-iodobenzylguanidine (MIBG), one of the most active agents used for the diagnosis and treatment of patients with relapsed or refractory neuroblastoma. The use of MIBG in neuroblastoma is predicated on the concept that the agent will selectively target NET expressing tumors or metastases and will not harm normal tissues, particularly those not expressing NET. In their proof-of-concept studies, the authors intentionally influenced the expression levels of NET in neuroblastoma cells *in vitro* and *in vivo* by the inhibition of histone deacetylation using vorinostat (suberoylanilidehydroxamic acid, SAHA) (More et al., 2011). Additional studies, currently ongoing, are required to confirm that selective partitioning of MIBG into neuroblastoma tumors by vorinostat administration can possibly achieve the desired efficacy from a lower dose of MIBG, and potentially mitigate the problematic hematologic toxicity often observed with this agent.

7. FUTURE DIRECTIONS

The family of solute carriers is increasingly recognized as having an important role in the pharmacokinetic and pharmacodynamic profiles of many anticancer drugs. Mechanistically, most of these drug-solute carrier interactions have been linked to either direct effect on tumoral exposure to the chemotherapeutic or indirect effects through a regulation of drug absorption and disposition patterns. The expression of many of the key drug-transporting solute carriers is now recognized to be polymorphic, and several variants may alter protein expression and/or function in key target tumors and organs in patients. Unfortunately, the

effects of these genetic variants in relation to potential phenotypical consequences are still largely unexplored for most substrates. Nonetheless, the few studies published to date have provided relatively consistent results and indicate an important inherited genetic contribution to solute carrier-mediated drug transport *in vivo*.

Considering the sheer magnitude of the number of transporters in humans identified thus far, it is not hard to imagine that the work done so far can only represent, at best, the tip of the iceberg. Furthermore, in the field of cellular sensitivity to substrate drugs, the functional and pharmacogenetic aspects of solute carrier expression in many malignant cells are still essentially unexplored. However, it is anticipated that, over the next decade, the importance of solute carriers with regard to the antitumor efficacy of chemotherapeutics will be more clearly defined. Collectively, continued investigation in this area will likely have a profound impact on attempts to further optimize and individualize treatment regimens involving substrate drugs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Transporters involved in the tumoral and systemic uptake or elimination of cisplatin and oxaliplatin. Solute carriers are in bold.

Figure 2. Transporters involved in the tumoral and systemic uptake or elimination of methotrexate. Solute carriers are in bold.

Table 1

Examples of anticancer drug transport by solute carriers

Drug	Influx Transporters	Efflux Transporters *	Citations
Bleomycin	SLC22A16 (OCT6)	N/A	(Aouida and Ramotar, 2010)
Capecitabine	SLC28A1 (hCNT1)	ABCA1	(Gonzalez-Haba et al., 2010; Mata et al., 2001)
Carboplatin	SLC31A1 (CTR1)	ATP7A	(Blair et al., 2009; Howell et al., 2010; Samimi et al., 2004)
Cisplatin	SLC22A1 (OCT1), SLC22A2 (OCT2), SLC31A1 (CTR1)	ABCC2, ABCC4, ATP7B, SLC47A1 (MATE1)	(Cui et al., 1999; More et al., 2010a; Nakamura et al., 2010; Safaei et al., 2008; Savaraj et al., 2003; Yonezawa et al., 2006; Zhang et al., 2010)
Cladribine	SLC28A1 (CNT1), SLC28A2 (CNT2), SLC28A3 (CNT3), SLC29A1 (ENT1)	ABCG2	(Badagnani et al., 2005; de Wolf et al., 2008; King et al., 2006; Owen et al., 2006)
Cytarabine	SLC28A1 (CNT1), SLC29A1 (ENT1), SLC29A2 (ENT2)	ABCC4, ABCC11	(Endo et al., 2007; Graham et al., 2000; Guo et al., 2009; Hubeek et al., 2005)
Dasatinib	N/A	ABCB1, ABCC4, ABCG2	(Dohse et al., 2010)
Daunorubicin	SLC22A4 (OCTN1)	ABCB1	(Kartner et al., 1983; Okabe et al., 2008)
Docetaxel	SLC22A7 (OAT2), SLC01B3 (OATP1B3)	ABCB1, ABCC2, ABCC10	(Franke et al., 2010a; Hopper-Borge et al., 2004; van Waterschoot et al., 2010; Yamaguchi et al., 2008)
Doxorubicin	SLC22A16 (OCT6), SLC22A4 (OCTN1)	ABCB1, ABCB5, ABCG2	(Frank et al., 2005; Hembruff et al., 2008; Okabe et al., 2005)
Epirubicin	N/A	ABCB1, ABCC1, ABCG2	(Hembruff et al., 2008)
Etoposide	SLC22A5 (OCTN2)	ABCB1, ABCC1, ABCC2	(Lagas et al., 2010; Wijnholds et al., 1998)
Fluorouracil	hNT1, SLC22A7 (OAT2)	N/A	(Kobayashi et al., 2005; Umemoto et al., 2009)
Gefitinib	N/A	ABCB1, ABCG2	(Agarwal et al., 2010)
Gemcitabine	SLC28A1 (CNT1), SLC29A1 (ENT1)	N/A	(Gusella et al., 2011)
Hydroxyurea	SLC01B3 (OATP1B3), SLC14A2 (UT-A), SLC14A1 (UT-B)	N/A	(Walker et al., 2011)
Ifosfamide	SLC22A2 (OCT2)	N/A	(Ciarimboli et al., 2011)
Imatinib	SLC21A3 (OATP1A2), SLC01B3 (OATP1B3), SLC22A1 (OCT1)	ABCB1, ABCC1, ABCC4, ABCG2	(Choi and Song, 2008; Eechoute et al., 2011b; Hu et al., 2008)
Irinotecan	SLC01B1 (OATP1B1)	ABCB1, ABCC2, ABCC4, ABCG2	(Bansal et al., 2009; Bessho et al., 2006; Candeil et al., 2004; Chen et al., 1999; Chu et al., 1997; Chu et al., 1999; de Jong et al., 2006; de Jong et al., 2007; Guo et al., 2010; Han et al., 2007; Innocenti et al., 2009; Iyer et al., 2002; Katayama et al., 2009; Kawabata et al., 2003; Luo et al., 2002; Nakatomi et al., 2001; Norris et al., 2005; Nozawa et al., 2005; Owatari et al., 2007; Sai et al., 2003; Sai et al., 2010; Shigeta et al., 2010; Smith et al., 2006; Sugiyama et al., 1998; Tagen et al., 2010; Takahata et al., 2008; Tian et al., 2005; Yamamoto et al., 2001)
Ixabipilone	N/A	ABCB1	(Shen et al., 2011)
Lapatinib	SLC01B1 (OATP1B1), SLC22A8 (OAT3)	ABCB1, ABCC10, ABCG2	(Kuang et al., 2010; Minematsu and Giacomini, 2011; Polli et al., 2008; Polli et al., 2009)
Melphalan	SLC7A5 (LAT1)	ABCB1	(Kuhne et al., 2009; Lin et al., 2004)

Drug	Influx Transporters	Efflux Transporters *	Citations
6-Mercaptopurine	SLC29A2 (ENT2), SLC22A7 (OAT2), SLC22A8 (OAT3)	ABCC4	(Fotoohi et al., 2006; Krishnamurthy et al., 2008; Mori et al., 2004; Nagai et al., 2007)
Mesna	SLC22A6 (OAT1), SLC22A8 (OAT3), SLC22A9 (OAT4)	ABCB1, ABCC2, SLC47A1 (MATE1)	(Cutler et al., 2011)
Methotrexate	SLC22A6 (OAT1), SLC22A7 (OAT2), SLC22A8 (OAT3), SLC22A9 (OAT4), SLC01A2 (OATP1A2), SLC01B1 (OATP1B1), SLC01B3 (OATP1B3), SLC04C1 (OATP4C1), SLC19A1, (RFC), SLC46A1 (PCFT)	ABCC1, ABCC2, ABCC3, ABCG2, ABCC4	(Badagnani et al., 2006; Cha et al., 2001; El-Sheikh et al., 2007; Han et al., 2010; Kitamura et al., 2008; Mikkaichi et al., 2004; Ni et al., 2010; Niemi et al., 2011; Rajgopal et al., 2001; Rothen et al., 2002; Unal et al., 2009; Yokooji et al., 2009; Zhao et al., 2009b; Zhao et al., 2008)
Mitoxantrone	SLC22A4 (OCTN1)	ABCB1, ABCG2	(Okabe et al., 2008; Pan and Elmquist, 2007; Shen et al., 2009)
Nilotinib	N/A	ABCB1, ABCG2	(Dohse et al., 2010; Haouala et al., 2010)
Oxaliplatin	SLC22A1 (OCT1), SLC22A2 (OCT2), SLC22A3 (OCT3)	SLC47A1 (MATE1), SLC47A1 (MATE2-K)	(Burger et al., 2010; Yonezawa et al., 2006; Zhang et al., 2006)
Paclitaxel	SLC22A7 (OAT2), SLC01B1 (OATP1B1), SLC01B3 (OATP1B3),	ABCB1, ABCC2, ABCC10	(Kobayashi et al., 2005; Lagas et al., 2006; Smith et al., 2005; Svoboda et al., 2011; Tanino et al., 2009; Yonezawa et al., 2006)
Pazopanib	N/A	ABCB1, ABCG2	(Keisner and Shah, 2011)
Rapamycin	N/A	ABCB1	(Oswald et al., 2010; Paine et al., 2004)
Sorafenib	N/A	ABCB1, ABCG2	(Agarwal et al., 2011; Flaherty et al., 2011)
Sunitinib	N/A	ABCB1, ABCG2	(Haouala et al., 2010; Tang et al., 2012)
Tamoxifen	N/A	ABCB1	(Iusuf et al., 2011; Teft et al., 2011)
6-Thioguanine	SLC28A3 (CNT3), SLC29A2 (ENT2), SLC22A8 (OAT3)	ABCC5	(Mori et al., 2004)
Topotecan	SLC22A8 (OAT3)	ABCB1, ABCC4, ABCG2	(Breedveld et al., 2007; Matsumoto et al., 2007b; Tian et al., 2006; Zhuang et al., 2006)
Vinblastine	N/A	ABCB1, ABCC1, ABCC2, ABCC10, ABCG2	(Hopper-Borge et al., 2004; Huisman et al., 2005; Kolwankar et al., 2005)
Vincristine	N/A	ABCB1, ABCC1, ABCC2, ABCC10	(Borst et al., 2000; Hopper-Borge et al., 2004; Kawabe et al., 1999)

* For ABC-mediated drug resistance review see (Szakacs et al., 2006)

Abbreviation: N/A, not available