Special Section on Transporters in Toxicity and Disease—Minireview

Uptake Carriers and Oncology Drug Safety^S

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ABSTRACT

Members of the solute carrier (SLC) family of transporters are responsible for the cellular influx of a broad range of endogenous compounds and xenobiotics in multiple tissues. Many of these transporters are highly expressed in the gastrointestinal tract, liver, and kidney and are considered to be of particular importance in governing drug absorption, elimination, and cellular sensitivity of specific organs to a wide variety of oncology drugs. Although the majority of studies on the interaction of oncology drugs with SLC have been restricted to the use of exploratory in vitro model systems, emerging evidence suggests that several

SLCs, including OCT2 and OATP1B1, contribute to clinically important phenotypes associated with those agents. Recent literature has indicated that modulation of SLC activity may result in drug-drug interactions, and genetic polymorphisms in SLC genes have been described that can affect the handling of substrates. Alteration of SLC function by either of these mechanisms has been demonstrated to contribute to interindividual variability in the pharmacokinetics and toxicity associated with several oncology drugs. In this report, we provide an update on this rapidly emerging field.

Introduction

The cellular membrane lipid bilayer is an effective and complex barrier that prevents the movement of many molecules, including drugs used in oncology, into cells. For this reason, evolutionary processes have developed membrane transport proteins to regulate movement of endogenous compounds that are required to maintain cellular function. This movement is commonly reliant on the action of a class of membrane proteins known as solute carriers (SLCs), which have received a great deal of attention due to accruing evidence that many drugs can accumulate inside cells by “hitchhiking” on these transporters. In fact, the contribution of transporter-mediated uptake of xenobiotics is now believed to be the predominant mechanism of intracellular accumulation (Dobson and Kell, 2008). Based on this principle, it is likely that many oncology drugs require specific transporter proteins to gain intracellular access in tumor cells to generate desired therapeutic effects, and thus that interindividual differences in the expression and/or function of transporters can contribute to variability in response to treatment. Similarly, SLCs also likely regulate accumulation of oncology drugs into normal healthy tissues and thereby directly contribute to drug-induced toxicity. Moreover, the ability of drugs to compete for the natural substrates of these transporters can potentially lead to altered cellular function and trigger unwanted adverse reactions. Considering that the clinical use of

virtually all currently used oncology drugs is associated with toxic side effects that limit the dose that can be safely administered and, in some cases, cause life-threatening toxicities associated with organ damage, knowledge of specific transporters and the extent of oncology drug substrate specificity can theoretically contribute to the development of improved strategies or the design of cotherapies that ameliorate the incidence and/or severity of these effects.

Currently, there are still only a few reports demonstrating that specific SLCs can modulate cellular accumulation of oncology drugs (Supplemental Table 1), and most studies have been performed in cell-based model systems involving mammalian or amphibian cells that are engineered to overexpress a single or, at best, a limited number of transporters. The continual identification of oncology substrates for SLCs using these heterologous in vitro expression systems provides valuable information for predicting drug-drug and drug-protein interactions. However, the well recognized limitation of these preliminary determinations is that they do not indicate the true relevance of a transporter in handling a substrate in the context of whole-body disposition. Indeed, to attribute an abnormality in normal physiology or oncology drug-induced phenotypes to transporter perturbation, the relevance of the transporter to the tissue-specific distribution of a drug must first be determined in vivo. The availability of rodent models for many SLCs that have been associated with the transport of oncology drugs is now providing an opportunity to close the in vitro–in vivo knowledge gap. In the present article, we provide an overview of this rapidly emerging field for commonly used oncology drugs, emphasize recently explored translational approaches, and discuss strategies that can be used to avoid drug-induced damage to healthy tissues.

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ABBREVIATIONS: Ara-C, cytarabine; CNT1/3, concentrating nucleoside transporter 1 or 3; CTR1, copper transporter 1; ENT1, equilibrative nucleoside transporter 1; MATE1/2-K, multidrug toxin and extrusion protein 1 or 2-K; MTX, methotrexate; OAT1/2/3, organic anion transporter 1, 2, or 3; OATP1B1/2/3, organic anion transporting polypeptides family 1B1, 2, or 3; OCT1/2, organic cation transporter 1 or 2; OCTN1/2, organic cation transporter novel type 1 or 2; RFC, reduced folate carrier; SLC, solute carrier; TKI, tyrosine kinase inhibitor.

Platinum Chemotherapeutics

Cisplatin is among the most widely used chemotherapeutic drugs and has significantly improved outcome in various human malignancies, such as those in patients with head and neck (Chitapanarux et al., 2010), testicular (Nichols and Kollmannsberger, 2011), lung (Ardizzoni et al., 2007), and ovarian cancer (Matei et al., 2009). Additionally, use of oxaliplatin has led to significantly improved outcome in patients with advanced or metastatic colorectal cancer (Goldberg et al., 2004). Both platinum drugs share structural similarities and are thought to primarily exert their antitumor properties by their ability to form inter- or intrastrand cross-links with DNA (Zwelling et al., 1979). Unfortunately, use of these agents is limited by debilitating off-target effects that vary significantly in both severity and time of onset between individual patients. Patients treated with cisplatin are at a high risk of toxicities originating from severe renal tubular damage (up to 41% of patients; the major dose limiting toxicity) (de Jongh et al., 2003), as well as from irreversible bilateral hearing loss (22–70% of patients) (Ruggiero et al., 2013), and a chronic neurotoxicity characterized by numbness and tingling, paresthesia, reduced deep-tendon reflexes, and leg weakness (up to 50% of patients) (van den Bent et al., 2002). Despite structural similarities, the use of oxaliplatin is almost exclusively limited by the onset of peripheral neurotoxicity, which can manifest as an acute and/or a chronic form. The acute neurotoxicity occurs in up to 92% of patients but quickly resolves, whereas the chronic form is similar to that seen in patients treated with cisplatin (McWhinney et al., 2009). Although the mechanisms responsible for these toxicities remain poorly understood, accumulating evidence has shown that particular SLCs play dominant roles in facilitating movement of these agents into the affected organs.

Several decades ago, investigations revealed that cisplatin preferentially accumulates in human renal cortex against a concentration gradient and could competitively inhibit uptake of the cation tetraethylammonium in mouse kidney slices or basolateral membrane vesicles of the renal cortex (Weiner and Jacobs, 1983; Nelson et al., 1984; Williams and Hottendorf, 1985), as well as inhibit the renal clearance of organic cations

from the basolateral site in isolated perfused rat kidneys (Miura et al., 1987). After further study, it was established that the organic cation transporter 2 (OCT2; encoded by the gene *SLC22A2*) is highly expressed at the basolateral membrane of proximal tubules (Fig. 1), and that both the murine and human homologs of this protein could mediate cellular uptake of cisplatin in vitro (Yokoo et al., 2007; Tanihara et al., 2009; Burger et al., 2010). Following these results, it was shown that OCT2 mediates cisplatin-induced renal damage in vivo using mice deficient in both Oct2 and the redundant murine transporter Oct1. These animals have decreased elimination of cisplatin via urinary excretion and are also protected from cisplatin-induced nephrotoxicity (Filipski et al., 2009). These findings were further expanded to show that patients with a reduced functional variant of OCT2 (c.808G>T) are protected from cisplatin-induced nephrotoxicity. This observation has since been replicated using an independent cohort of patients (Iwata et al., 2012). The implications of these findings have since generated promising clinical applications, given that expression of OCT2 appears to be absent in most tumors (Franke et al., 2010b; Sprowl et al., 2013a). Collectively, it therefore appears possible to decrease cisplatin-induced nephrotoxicity via pharmacological inhibition of OCT2 function without sacrificing the antitumor efficacy of cisplatin. In fact, promising studies have already been conducted demonstrating that concurrent administration of cisplatin with the OCT2 inhibitor cimetidine (Zhang et al., 1998; Urakami et al., 2002; Franke et al., 2010b) can offer at least partial protection against renal toxicity (Sleijfer et al., 1987; Ciarimboli et al., 2010) without altering antitumor efficacy in either murine models or humans (Katsuda et al., 2010; Sprowl et al., 2013b). Nonetheless, it is important to point out that cimetidine has an inhibition constant (K_i) that is comparable to OCT2 for two solute carriers expressed on the luminal membrane of renal tubular cells, the multidrug and toxin extrusion protein 1 (MATE1) and MATE2-K (Koepsell et al., 2007; Matsushima et al., 2009; Ohta et al., 2009; Tsuda et al., 2009). Although a genetic polymorphism of MATE1 (rs2289669 G>A) associated with reduced function has been reported to have no impact on cisplatin-induced nephrotoxicity in patients (Iwata

Fig. 1. Solute carriers known to regulate accumulation of cisplatin or oxaliplatin into tissues associated with drug toxicity. The organic cation transporter OCT2 is expressed in the cochlea, dorsal root ganglia (DRG), and kidney, and mediates uptake while the multidrug and toxin extrusion proteins MATE1 and MATE2-K remove cisplatin and oxaliplatin from proximal tubule cells.

et al., 2012), loss of Mate1 function in mice has led to increased cisplatin-induced renal tubular damage (Nakamura et al., 2010). Likewise, the 5-hydroxytryptamine-3 receptor antagonist ondansetron, which has been shown to inhibit the function of OCT2 and MATEs, can potentiate cisplatin-induced nephrotoxicity in mice by preferentially inhibiting Mate1 function and increasing accumulation of cisplatin into proximal tubular cells (Li et al., 2013). Regardless, the use of cimetidine currently remains a viable option as the previous *in vivo* studies indicate protective effects rather than potentiating toxicity, although the use of other inhibitors could be explored to circumvent this problem. In fact, the tyrosine kinase inhibitor (TKI) imatinib has been identified as a potent, noncompetitive inhibitor of OCT2, and its use appears to protect rats from cisplatin-induced nephrotoxicity by preventing platinum accumulation into the kidney (Tanihara et al., 2009; Franke et al., 2010b).

In addition to the connection of OCT2 with cisplatin-induced nephrotoxicity, there is current evidence to suggest that this transporter is also involved in the etiology of other toxicities associated with platinum drugs. For example, OCT2 is expressed in the inner ear, and mice lacking Oct1 and Oct2 or wild-type mice receiving cimetidine as a transporter inhibitor are protected from cisplatin-induced hearing loss (Ciarimboli et al., 2010). The clinical relevance of these findings remains currently unknown. Similarly, a recent study demonstrated that OCT2 is also a modulator of platinum-induced neurotoxicity, in particular, the neurotoxicity associated with oxaliplatin. In patients, oxaliplatin does not induce renal or ototoxic damage to a significant extent. However, like cisplatin, oxaliplatin accumulates at relatively high levels within dorsal root ganglia of the peripheral nervous system, which is the initial trigger leading to peripheral neuropathy (Holmes et al., 1998; Screnci et al., 2000; McDonald et al., 2005). Oxaliplatin is a substrate for OCT2, and this SLC was recently found to be expressed at high levels in both murine and human dorsal root ganglia (Yonezawa et al., 2006; Burger et al., 2010; Sprowl et al., 2013a). In fact, genetic or pharmacological inhibition of Oct2 function protects mice from acute oxaliplatin-induced neuropathy and, like cisplatin, decreases urinary elimination without altering systemic concentrations (Sprowl et al., 2013a). Further studies are currently underway to assess whether inhibition of OCT2 function will ameliorate chronic forms of cisplatin- and oxaliplatin-induced neuropathy, as well as to assess the clinical applications of this strategy. It is worth pointing out that probenecid, an

organic anion that does not inhibit OCT2, can significantly reduce the tubular secretion of cisplatin without affecting glomerular filtration, and that this leads to reduced nephrotoxicity (Ross and Gale, 1979; Jacobs et al., 1984, 1991; Klein et al., 1991). Although the underlying mechanism for this interaction is unclear, it is conceivable that anionic platinum-sulfhydryl complexes formed from cisplatin in the γ -glutamyltranspeptidase pathway accumulate in kidney cells through an organic anion transport mechanism that is probenecid-sensitive, possibly organic anion transporter 1 (OAT1) or OAT3.

There are other SLCs that are possibly involved in side effects associated with platinum-based oncology drugs (Table 1). In particular, the copper transporter 1 (CTR1; SLC31A1) has been implicated in the cellular uptake of all three approved platinum compounds, namely, cisplatin, oxaliplatin, and carboplatin (Larson et al., 2009). Expression of CTR1 has been reported in dorsal root ganglia of rats (Liu et al., 2009), the basolateral membrane of the proximal tubular cells (Pabla et al., 2009), and murine cochlea, although generally the expression levels are low in comparison with OCT2 (Ciarimboli et al., 2010). In line with expression patterns, studies performed in mice have demonstrated that reduced function of CTR1 is associated with amelioration of cisplatin-induced cell death in proximal tubules (Pabla et al., 2009), and that administration of copper sulfate, a competitive inhibitor of CTR1, with cisplatin protects against cisplatin-induced ototoxicity (More et al., 2010). Moreover, cells within the dorsal root ganglia that express high levels of CTR1 appear to be more susceptible to atrophy by platinum agents (Liu et al., 2009; Ip et al., 2010). However, more recent findings indicate that CTR1 may not be an important contributor to the neurotoxicity induced by oxaliplatin (Liu et al., 2013), and despite the previous promising findings, a direct clinical demonstration of CTR1 involvement in modulating platinum-induced toxicity remains lacking. Moreover, recent experimental evidence has been generated that questions the ability of CTR1 to regulate cisplatin uptake (Ivy and Kaplan, 2013). Clearly, additional investigation into the role of CTR1 and platinum-induced toxicity is required. In this context, it should be noted that CTR1 is expressed in multiple solid tumors, and that pharmacological inhibition of this transporter will possibly impair antitumor efficacy (Larson et al., 2009).

Several other transporters require additional exploration with *in vivo* models, such as organic cation transporter novel type 1 (OCTN1)

TABLE 1
Solute carriers associated with cellular accumulation of platinum chemotherapeutics

Drug [Alias]	Mechanism of Action	Principle Side Effects	Transporters	References
Carboplatin [Paraplatin]	Platination; DNA cross-linking	Nausea and vomiting Myelosuppression Neurotoxicity Electrolyte abnormalities Hypersensitivity reaction	SLC28A1 (CTR1) ^a	(Larson et al., 2009)
Cisplatin [Platinol]	Platination; DNA cross-linking	Nausea and vomiting Myelosuppression Neurotoxicity Electrolyte abnormalities Hypersensitivity reaction Renal toxicity Ototoxicity	SLC22A1 (OCT1) ^{a,b} SLC22A2 (OCT2) ^{a,b,c} SLC31A1 (CTR1) ^{a,b} SLC47A1 (MATE1) ^{a,b}	(Yokoo et al., 2007; Filipinski et al., 2009; Larson et al., 2009; Tanihara et al., 2009; Nakamura et al., 2010)
Oxaliplatin [Eloxatin]	Platination; DNA cross-linking	Nausea and vomiting Myelosuppression Neurotoxicity Hypersensitivity reaction Diarrhea	SLC22A1 (OCT1) ^a SLC22A2 (OCT2) ^{a,b} SLC22A3 (OCT3) ^a SLC22A4 (OCTN1) ^a SLC22A5 (OCTN2) ^a SLC31A1 (CTR1) ^a SLC47A1 (MATE1) ^a SLC47A2 (MATE2-K) ^a	(Yonezawa et al., 2006; Yokoo et al., 2007; Larson et al., 2009; Burger et al., 2010; Sprowl et al., 2013a)

^aEvidence of drug uptake being regulated by solute carriers *in vitro*.

^bEvidence of drug uptake being regulated by solute carriers *in vivo*.

^cEvidence of drug uptake being regulated by solute carriers in patient populations.

and OCTN2, which are expressed at detectable levels in the dorsal root ganglia and have been implicated in the transport of oxaliplatin in some (Jong et al., 2011) but not all studies (Yonezawa et al., 2005; Haschke et al., 2010; Lancaster et al., 2010). The main endogenous substrate of OCTN2 is carnitine (vitamin B₁₂; β -hydroxy- γ -trimethylaminobutyric acid), a hydrophilic zwitterion that plays an essential role in the transfer of long-chain fatty acids inside mitochondria for β -oxidation, and as such is critical in the production of cellular energy (Longo et al., 2006). Carnitine is normally maintained at a steady level in the blood via a rescue mechanism that involves reabsorption in the kidney of filtered carnitine by the solute carrier OCTN2 (SLC22A5) (Ohtani et al., 1984). The existence of this reabsorption mechanism for carnitine, as well as the occurrence of mutations in OCTN2 that lead to primary systemic carnitine deficiency, strongly supports the critical physiologic importance of OCTN2 (Scaglia et al., 1998). Indeed, metabolic abnormalities similar to human primary systemic carnitine deficiency have been described in juvenile visceral steatosis mice (Koizumi et al., 1988) and demonstrated to be caused by a null mutation (1114T>G; L352R) in the mouse *Ocn2* gene, *Slc22a5* (Lu et al., 1998). Furthermore, heterozygosity for OCTN2 mutations in humans is associated with an intermediate carnitine-deficiency phenotype, suggesting that even partial loss of transporter function may be detrimental. In this context, it is particularly noteworthy that, in a previous study involving a small cohort of adult patients, treatment with cisplatin was associated with a significant increase in the urinary excretion of carnitine, which eventually normalized about 7 days after discontinuing therapy (Heuberger et al., 1998). Similar observations have been made in patients undergoing combination chemotherapy with ifosfamide-doxorubicin-cisplatin (Hockenberry et al., 2009), paclitaxel-carboplatin, or vinorelbine-carboplatin (Mancinelli et al., 2007). In the case of cisplatin treatment, the increases in urinary carnitine were hypothesized to be due to inhibition of active tubular reabsorption of carnitine and acylcarnitines (Heuberger et al., 1998), and direct inhibition of OCTN2 has been reported for several oncology drugs, including actinomycin D (Ohashi et al., 1999), vinblastine (Diao et al., 2009), and etoposide (Hu et al., 2012). Unlike other agents previously linked with hypocarnitinemia, however, cisplatin-induced carnitine wasting is associated with an unusual regulatory mechanism likely involving deactivation of the peroxisome proliferator-activated receptor alpha (PPAR- α) transcription factor and

subsequent downregulation of OCTN2 (Lancaster et al., 2010). Additional studies are clearly warranted to further understand the pharmacodynamic and toxicological implications of oncology drugs affecting the carnitine-wasting phenomenon.

Methotrexate

Methotrexate (MTX) is an antifolate agent commonly used in the treatment of acute lymphoblastic leukemia, non-Hodgkin lymphoma, and osteosarcoma that acts by inhibiting the synthesis of folic acid required for nucleotide synthesis and subsequent cellular replication. When given at high doses, the clinical use of MTX becomes limited by the onset of a number of side effects, including neurotoxicity, hepatotoxicity, nephrotoxicity, and gastrointestinal mucositis, all of which are associated with accumulation of MTX and subsequent damage to normal tissues. Due to the frequency at which MTX is used as a chemotherapeutic agent, there have been numerous investigations aimed at evaluating the role of SLCs in these toxicities.

Although multiple transporters have been identified in regulating the uptake of MTX into cells (Fig. 2; Table 2), its movement across cellular membranes is most commonly linked to the reduced folate carrier (RFC; SLC19A1). Considering that MTX is an antifolate, it is not surprising that cellular uptake is mediated by RFC, and that activity of RFC has been associated with treatment efficacy (Fischer, 1962; Gorlick et al., 1996; Sowers et al., 2011). Unfortunately, studies are limited in demonstrating a role of RFC in regulating MTX toxicity, although it is known that the gene encoding RFC is located on chromosome 21q22.3 and children with trisomy 21 are more susceptible to adverse events in response to therapy with MTX (Garre et al., 1987; Dixon et al., 1994; Williams and Flintoff, 1995; Yang-Feng et al., 1995; Buitenkamp et al., 2010). Whether these events are a result of a gene dosage effect leading to increased activity in RFC and cellular uptake of MTX has yet to be demonstrated. The c.80G>A variant, which is thought to increase function of RFC, has been associated with increased incidences of MTX-induced toxicity, including hepatotoxicity in patients with psoriasis (Campalani et al., 2007) and with a higher degree of bone marrow and liver toxicity in patients with acute lymphoblastic leukemia (Gregers et al., 2010). However, multiple studies have also reported that this variant has no effect on toxicity after MTX treatment (Kishi et al., 2003; Shimasaki et al., 2006; Huang et al.,

Fig. 2. Solute carriers known to regulate accumulation of methotrexate into tissues associated with drug toxicity. The organic anion transporting polypeptides OATP1B1 and OATP1B3 are expressed in human hepatocytes. The organic anion transporters OAT1 and OAT2 are expressed at the basolateral membrane of proximal tubule cells within the kidney and are likely key regulators of methotrexate clearance and nephrotoxicity.

TABLE 2
Solute carriers associated with cellular accumulation of methotrexate

Drug [Alias]	Mechanism of Action	Principle Side Effects	Transporters	References
Methotrexate [Trexall]	Interferes with folate metabolism	Myelosuppression Mucositis Dermatological toxicity (skin rash and/or nail changes) Renal toxicity Neurotoxicity	SLC22A6 (OAT1) ^a SLC22A7 (OAT2) ^a SLC22A8 (OAT3) ^{a,b} SLC22A9 (OAT4) ^a SLCO1A2 (OATP1A2) ^{a,b} SLCO1B1 (OATP1B1) ^{a,b,c} SLCO1B3 (OATP1B3) ^{a,b} SLCO4C1 (OATP4C1) ^a SLC19A1 (RFC) ^{a,c} SLC46A1 (PCFT) ^a	(Abe et al., 1999; Sun et al., 2001; Takeda et al., 2002; Mikkaichi et al., 2004; Mori et al., 2004; Badagnani et al., 2006; van de Steeg et al., 2009, 2013; Zhao et al., 2009; Sowers et al., 2011)

^aEvidence of drug uptake being regulated by solute carriers in vitro.

^bEvidence of drug uptake being regulated by solute carriers in vivo.

^cEvidence of drug uptake being regulated by solute carriers in patient populations.

2008; Chandran et al., 2010; Faganel Kotnik et al., 2010; Chiusolo et al., 2012), suggesting that additional comprehensive studies are required to definitively determine the role of RFC for this drug.

Regardless of the importance of RFC, there are several other transporters that modulate cellular accumulation of MTX, including the organic anion transporters OAT1, OAT2, and OAT3 (Sun et al., 2001; Mori et al., 2004). Renal elimination is the major route of MTX clearance, and since OAT1 and OAT3 are both expressed along the basolateral membrane of proximal tubule cells, they are likely regulators of renal clearance and MTX-induced nephrotoxicity (Sweet et al., 1997, 2003). This notion is consistent with in vivo evidence showing that mice with an OAT3 deficiency have significantly delayed clearance of methotrexate (VanWert and Sweet, 2008), although a direct connection with toxicity remains uncertain. In addition to OAT1 and OAT3, several hepatic organic anion transporting polypeptides (OATPs), including OATP1B1 (SLCO1B1), OATP1B3 (SLCO1B3), and OATP1A2 (SLCO1A2) (Abe et al., 1999; Badagnani et al., 2006), are involved in cellular uptake of MTX. Of these transporters, OATP1A2 in the liver is expressed in cholangiocytes and not in hepatocytes (Lee et al., 2005), and the direct contribution of this transporter to the disposition of MTX is unclear (van de Steeg et al., 2013). Unlike OATP1B1 and OATP1B3, OATP1A2 is also expressed in the epithelial cells at the blood-brain barrier and on the distal tubule cells of the kidney, where it may contribute to MTX-related toxicities observed in the central nervous system and kidney (Bronger et al., 2005; Lee et al., 2005). Follow-up in vivo studies are required to address these hypotheses.

Among the transporters associated with MTX, the role of OATP1B1 in its disposition profile has been most clearly established. The first in vivo studies demonstrating a role of OATP1B1 in modulating MTX disposition were performed in humanized transgenic mice expressing human OATP1B1, and these animals have reduced systemic levels of MTX and increased liver-to-plasma ratios (van de Steeg et al., 2009, 2013). Interestingly, similar results were observed in mice over-expressing human OATP1B3. These findings are consistent with the notion that several inherited variants in these SLCs are associated with altered clearance of MTX in patients, as well as with increased gastrointestinal toxicity (Trevino et al., 2009; Lopez-Lopez et al., 2011). The association of the same variants with altered MTX clearance and toxicity has since been replicated in follow-up studies (Radtko et al., 2013; Ramsey et al., 2013). Additional rare variants of this SLC, including those with damaging function, have also been associated with further decreased clearance of MTX (Ramsey et al., 2012). However, since hepatobiliary excretion of MTX in humans is only a minor pathway of elimination, the overall contribution of OATP1B-transporter genotypes to explaining interindividual variability in MTX clearance is relatively modest (<15%). Therefore, the main contributing factors underlying genetic predisposition to low MTX clearance in humans are currently unclear, indicating that regular monitoring of MTX plasma

concentrations remains warranted to prevent the occurrence of unwanted toxicities. Moreover, further studies are warranted to assess the physiologic roles of other transporters that have been associated with cellular uptake of methotrexate in vitro, such as OAT4, OATP4C1, and the proton-coupled folate transporter (PCFT) (Table 2) (Takeda et al., 2002; Mikkaichi et al., 2004; Zhao et al., 2009).

Nucleoside Analogs

Analogues of nucleosides have been used as a common therapeutic strategy for the treatment of various types of cancers. These agents include cytarabine (Ara-C), used primarily in the treatment of acute myeloid leukemia, as well as gemcitabine, used in the treatment of pancreatic cancer. The clinical use of Ara-C has been associated with severe adverse effects, some of which can prove fatal, including anemia, neutropenia, thrombocytopenia, renal impairment, stomatitis, and acute pulmonary syndrome (Reykdal et al., 1995; Cole and Gibson, 1997; Briassoulis and Pavlidis, 2001). Moreover, high-dose Ara-C treatment is known to initiate peripheral neuropathy, encephalopathy and cerebellar dysfunction, paraplegia, as well as ataxia, nystagmus, and dysarthrias, which typically occur within 3–7 days after treatment (Lazarus et al., 1981; Winkelman and Hines, 1983; Herzig et al., 1987). Gemcitabine has also been associated with numerous adverse events, including the onset of anemia, neutropenia, thrombocytopenia, pulmonary toxicity, as well as hepatic and renal impairment (Koczor et al., 2012).

Not surprisingly, expression of the human equilibrative nucleoside transporter 1 (ENT1; SLC29A1) is known to regulate cellular uptake of Ara-C. In fact, ENT1 is reported to regulate up to 80% of Ara-C uptake into target cells at plasma concentrations of 0.5–1 μ M, which are readily achieved at even standard low-dose regimens (Sundaram et al., 2001; Clarke et al., 2002). Acute myeloid leukemia patients with blasts negative for ENT1 expression experience a shorter disease-free survival (7.7 vs. 13 months) and are at an 8-fold increased risk of early relapse (Galmarini et al., 2002). Moreover, high expression of ENT1 is associated with increased survival in patients with pancreatic ductal adenocarcinoma and cholangiocarcinoma treated with gemcitabine (Kobayashi et al., 2012; Marechal et al., 2012). In addition to associations with antitumor effects, coadministration of Ara-C with an ENT1 inhibitor has been shown to decrease toxicity in peripheral blood mononuclear cells (Parmar et al., 2011). ENT1 has low genetic variability with currently no known functional variants found in the coding region (Osato et al., 2003), although there is one particular variant located in the transcription factor binding region at $-706\text{G}>\text{C}$, which has an allelic frequency of 0.2 in Caucasians and is thought to increase mRNA expression in peripheral blood cells (Myers et al., 2006). Unfortunately, patients with this variant have only a modest 1.1-fold increase in ENT1 expression, and there appears to be no correlation with Ara-C–induced hematologic toxicity (Parmar et al., 2011).

ENT1 is also known to regulate cellular uptake of gemcitabine, and recent studies have identified another genetic variant of ENT1 (913C>T) as being associated with severe (grade 3–4) neutropenia in patients with locally advanced pancreatic cancer following treatment with gemcitabine (Tanaka et al., 2010). Interestingly, this result was not observed in an earlier study by the same investigators (Okazaki et al., 2010), indicating that further studies are required to confidently assess the role of ENT1 in modulating nucleoside analog safety in patients.

In addition to ENT1, there are other nucleoside transporters that have been implicated in regulating cellular uptake of nucleoside analogs as well as modulating response and the onset of adverse events (Table 3). The concentrating nucleoside transporter 1 (CNT1; SLC28A1) has been shown to mediate transport of gemcitabine and Ara-C (Graham et al., 2000). In fact, patients with an SLC28A1 c.1561G>A genetic variant who received gemcitabine experienced significantly higher rates of neutropenia and thrombocytopenia (Soo et al., 2009), which is likely due to an increased intracellular influx of gemcitabine in bone marrow progenitors. CNT3 has also been identified in regulating nucleoside analog uptake, although to a lesser degree compared with ENT1 (Ritzel et al., 2001). Nonetheless, it has been shown that 42.3% of patients with a certain CNT3 genetic variant experienced grade 3–4 neutropenia following treatment with gemcitabine, compared with only 25.7% of patients with the wild-type or heterozygous genotype ($P = 0.035$) (Tanaka et al., 2010). Unfortunately, considering the lack of replication in multiple studies as well as the lack of in vitro analysis to assess the impact that these variants have on nucleoside transporter function, there is still much work to be done in this field.

Taxanes

Paclitaxel, docetaxel, and cabazitaxel are members of the taxane family of agents used in the treatment of many malignancies, including breast, lung, ovarian, prostate, and gastric cancers. Taxanes interact with

tubulin and prevent their dissociation, which in turn prevents chromosomal segregation, leading to a cell cycle arrest in G2/M and subsequent promotion of apoptosis (Ringel and Horwitz, 1991; Chazard et al., 1994). Clinical use of all three approved taxanes is limited by a relatively narrow therapeutic window that, when exceeded, can lead to the onset of various side effects, including peripheral neuropathy and severe bone marrow depression, in particular neutropenia. In fact, neutropenia is considered the major dose-limiting toxicity, and severe (grade 3 or 4) neutropenia occurs in up to 88% of patients who receive docetaxel (Rougier et al., 2000; Ishimoto et al., 2006), depending on the patient's disease type. Due to their common use in the clinic, there have been many studies conducted to investigate potential transporters that can modulate uptake of taxanes. Some correlations of hematologic and neurologic toxicities with transporter expression or function have been made, although these studies have been mostly limited to members of the ATP-binding cassette protein family (Sissung et al., 2006, 2008).

Despite intense efforts, there have been no direct correlations made between SLCs and the incidence and severity of neurologic toxicities, which demonstrates that this field remains in its infant stages. Nonetheless, strong evidence exists to demonstrate that specific SLCs can indirectly influence drug-induced hematologic toxicities by modulating the systemic clearance of taxanes. Both paclitaxel and docetaxel have been identified as a substrate of OAT2 (SLC22A7), OATP1B1, and OATP1B3 (Fig. 3; Table 4) (Smith et al., 2005; Franke et al., 2010a; Svoboda et al., 2011; van de Steeg et al., 2011; de Graan et al., 2012). Studies performed in transfected cells have shown that paclitaxel and docetaxel are also transported substrates of the functionally related mouse transporter Oatp1b2 (Slco1b2), but this was not noted under the same experimental conditions for cabazitaxel. The lack of transport of cabazitaxel by Oatp1b2 is somewhat surprising considering its structural similarity with docetaxel, both having a 10-deacetylbaicatin III backbone (Vrignaud et al., 2013), and because cabazitaxel has been reported to inhibit OATP1B1 and

TABLE 3
Solute carriers associated with accumulation of nucleoside analogs

Drug [Alias]	Mechanism of Action	Principle Side Effects	Transporters	References
Cytarabine [Cytosar; Ara-C, cytosine arabinoside]	Incorporated into DNA; inhibits DNA polymerase; terminates DNA chain elongation	Myelosuppression Nausea and vomiting Mucositis Gastrointestinal (ulcers, pancreatitis) Hyperuricemia Dermatological toxicity (skin rash and/or nail changes) Hand-foot syndrome Peripheral edema Conjunctivitis Neurotoxicity Hepatotoxicity	SLC28A1 (CNT1) ^a SLC29A1 (ENT1) ^a	(Graham et al., 2000; Sundaram et al., 2001)
Gemcitabine [Gemzar]	Incorporated into DNA; inhibits DNA polymerase; terminates DNA chain elongation; inhibits ribonucleotide reductase (prodrug)	Myelosuppression Nausea and vomiting Mucositis Diarrhea Fever Flu-like symptoms Dermatological toxicity (skin rash and/or nail changes) Neurotoxicity Peripheral edema Hepatotoxicity Renal toxicity	SLC28A1 (CNT1) ^{a,b} SLC29A1 (ENT1) ^{a,b} SLC28A3 (CNT3) ^{a,b}	(Graham et al., 2000; Ritzel et al., 2001; Soo et al., 2009; Tanaka et al., 2010)

^aEvidence of drug uptake being regulated by solute carriers in vitro.

^bEvidence of drug uptake being regulated by solute carriers in patient populations.

OATP1B3, albeit at relatively high concentrations (Jevtana prescribing information; see <http://products.sanofi.us/jevtana/jevtana.pdf>).

Since hepatic metabolism is the dominant elimination mechanism of docetaxel (mediated by CYP3A4) and paclitaxel (mediated by CYP2C8 and CYP3A4), it is not surprising that OATP1B-type transporters, which are exclusively expressed at the basolateral membrane of hepatocytes, were identified as SLCs regulating their liver uptake. So far, only one study has identified OATP1B1 as a transporter of paclitaxel in which it was demonstrated that SLC overexpressing *Xenopus laevis* oocytes accumulated higher levels of paclitaxel, and that OATP1B1-overexpressing SKOV-3 cells were more sensitive to paclitaxel-induced cytotoxic effects compared with cells transfected with an empty control vector (Svoboda et al., 2011). However, these findings are in conflict with other reports in which uptake of paclitaxel was evaluated in similar heterologous expression models. Studies performed in transgenic mice expressing OATP1B1 in hepatocytes have confirmed the relatively minor contribution of this SLC to the disposition of paclitaxel, and these findings collectively support the possibility that OATP1B1 is a high-affinity transporter that becomes saturated at plasma concentrations associated with even relatively low doses of the drug (Smith et al., 2005; van de Steeg et al., 2011). Similar discrepancies in OATP1B1 transporter affinity have been reported for docetaxel (Baker et al., 2009; de Graan et al., 2012).

Based on recently performed in vitro uptake studies (de Graan et al., 2012), multiple functionally different haplotypes, including OATP1B1*5 and OATP1B1*15, were found to have a detrimental impact on docetaxel transport. This finding is consistent with previous studies showing substantially diminished transport activity of several OATP1B1 substrates by these particular variants when transfected into mammalian cells (Kameyama et al., 2005), and these variants have also been associated with altered systemic exposure and toxicity in response to multiple substrate drugs (Niemi et al., 2011). Interestingly, the relevance of these genetic variants in OATP1B1 could not be confirmed in a pharmacogenetic-association study performed in Caucasian patients

(de Graan et al., 2012). It is possible that additional rare genetic variants or haplotypes in OATP1B1 of importance to the transport docetaxel in this population are yet to be discovered, and that much larger numbers of patients are then needed to more precisely quantify genotype-phenotype associations. In the same study, several genetic variants in OATP1B3 were also not significantly associated with the pharmacokinetics of docetaxel. This is in line with an earlier report (Baker et al., 2009), although the findings are at odds with several other investigations performed in patients of Asian descent. For example, homozygosity (GG) for rs11045585 was associated with reduced clearance of docetaxel, compared with patients carrying the AA or AG genotypes (Chew et al., 2011). In another study, a particular OATP1B3 genotype combination comprising the reference allele at IVS4+76G>A (rs4149118) and variant alleles at c.699G>A (rs7311358), IVS12+5676A>G (rs11045585), and *347-*348insA (rs3834935) was also linked with reduced clearance of docetaxel (Chew et al., 2012). It is possible that differences in outcome with the study by de Graan et al. are associated with the fact that such variants may occur at different frequencies between Asians and Caucasians, and/or on different, ethnicity-dependent haplotype structures.

Regardless of any potential ethnic considerations, the existence of at least two potentially redundant uptake transporters in the human liver with similar affinity for agents such as paclitaxel and docetaxel supports the possibility that functional defects in both of these proteins may be required to confer substantially altered disposition phenotypes such as those seen in *Oatp1b*-deficient mice. Although complete functional deficiency of either OATP1B1 or OATP1B3 has been recorded to occur (Kim et al., 2007), deficiency of both transporters is extremely rare, with an estimated frequency in the human population of about 1 in a million (van de Steeg et al., 2012). It can thus be postulated that intrinsic physiologic and environmental variables influencing OATP1B1- or OATP1B3-mediated uptake of taxanes into hepatocytes may have a more profound influence on clearance than do defective genetic variants. This recognition is particularly relevant in

Fig. 3. Solute carriers known to regulate accumulation of taxanes into tissues associated with drug accumulation. The organic anion transporting polypeptides OATP1B1 and OATP1B3 are expressed in human hepatocytes. OATP1B1 and OATP1B3 modulate uptake of paclitaxel and docetaxel and loss of function increases systemic exposure, which can lead to induction of devastating adverse events. The organic anion transporter OAT2 is also expressed in human hepatocytes and loss of function or expression can also lead to increased systemic exposure of taxanes.

TABLE 4
Solute carriers associated with cellular accumulation of taxanes

Drug [Alias]	Mechanism of Action	Principle Side Effects	Transporters	References
Docetaxel [Taxotere]	Microtubule depolarization inhibitor	Myelosuppression Hypersensitivity reaction Alopecia Neurotoxicity Dermatological toxicity (skin rash and/or nail changes) Mucositis	SLC22A7 (OAT2) ^{a,b} SLC01B1 (OATP1B1) ^{a,b,c} SLC01B3 (OATP1B3) ^{a,b,c}	(Franke et al., 2010a; de Graan et al., 2012)
Paclitaxel [Taxol; Abraxane]	Microtubule depolarization inhibitor	Myelosuppression Hypersensitivity reaction Alopecia Neurotoxicity Dermatological toxicity (skin rash and/or nail changes) Mucositis Cardiotoxicity	SLC22A7 (OAT2) ^a SLC01B1 (OATP1B1) ^{a,b} SLC01B3 (OATP1B3) ^{a,b}	(Smith et al., 2005; Svoboda et al., 2011; van de Steeg et al., 2011)

^aEvidence of drug uptake being regulated by solute carriers in vitro.

^bEvidence of drug uptake being regulated by solute carriers in vivo.

^cEvidence of drug uptake being regulated by solute carriers in patient populations.

the context of the recent guidelines offered by The International Transporter Consortium regarding preclinical criteria needed to trigger the conduct of clinical studies to evaluate drug-transporter interactions (Giacomini et al., 2010). Indeed, it is conceivable that instances of idiosyncratic hypersensitivity to taxanes are the result of currently unrecognized drug-drug interactions at the level of hepatocellular uptake mechanisms.

To add further to the complexity of the disposition properties of taxanes, the solubilizers Kolliphor EL (formerly Cremophor EL; used for paclitaxel) and polysorbate 80 (used for docetaxel and cabazitaxel) were recently found to strongly inhibit the uptake of OATP1B1 and OATP1B3 substrates into cells overexpressing the transporters (de Graan et al., 2012; Engel et al., 2012). Although further investigation is required to confirm direct involvement of solubilizer-mediated inhibition of OATP1B1 and OATP1B3 as the primary mechanistic basis for the apparent lack of observed in vivo effects of genetic variants, it is of note that similarly altered, solubilizer-dependent hepatic uptake has also been described for colchicine in the presence of Solutol HS15 (Bravo Gonzalez et al., 2004). These observations suggest that the impact of reduced-function variants of OATP1B1 and OATP1B3 on the clearance of taxanes may be much more pronounced for solubilizer-free formulations of the drugs, such as nab-paclitaxel (ABI-007; Abraxane) and nab-docetaxel (ABI-008).

In this context, it is of interest to point out that OATP1B-type transporters, in particular OATP1B3, are expressed at relatively high levels in tumors of the colon, endometrium, esophagus, lung, prostate, stomach, testis, and bladder (Lancaster et al., 2013), and that both OATP1B1 and OATP1B3 contribute to the in vitro cytotoxicity of taxanes in ovarian cancer cells (Svoboda et al., 2011). Although systemic exposure to free (unbound) taxanes is believed to be the dominant driver of drug-induced cytotoxicity at tumor sites (Ait-Oudhia et al., 2012), it is conceivable that these transporters can contribute directly to tumoral drug uptake, and that this process can be inhibited by solubilizers such as Kolliphor EL and polysorbate 80, leading to diminished antitumor activity. This possibility would be consistent with available clinical data on the comparative efficacy of the various paclitaxel formulations (reviewed in Ait-Oudhia et al., 2012), and with preclinical findings suggesting that the absorption rate constant of paclitaxel uptake into tumors is dramatically decreased in the presence of Kolliphor EL compared with nab-paclitaxel (Desai et al., 2006), and that a tumor-delivery mechanism exists for nab-paclitaxel that is independent of secreted protein acidic and rich in cysteine (SPARC)

(Neesse et al., 2013), a matricellular glycoprotein produced by tumors and/or neighboring stroma that facilitates the intracellular accumulation of intact albumin nanoparticles (Yardley, 2013).

In addition to the OATP1B-transporter family, docetaxel and paclitaxel are known substrates of the organic anion transporter OAT2 (Kobayashi et al., 2005; Baker et al., 2009), which may also play a role in hepatic uptake of these drugs. Using a rat model, castration has been shown to increase OAT2 expression in the liver and increase hepatic uptake of docetaxel, leading to an increased elimination. This observation is in line with findings in human patients with prostate cancer, where chemical or surgical castration is associated with dramatically increased clearance of docetaxel by a mechanism that is unrelated to altered activity of hepatic CYP3A4 (Franke et al., 2010a). This suggests that the decreased incidence of neutropenia in castrated patients with prostate cancer following docetaxel-based chemotherapy (Petrylak et al., 2004; Tannock et al., 2004; Hussain et al., 2005; Taplin et al., 2006; Rathkopf et al., 2008) is possibly due to increased hepatic uptake of docetaxel, leading to a decrease in systemic exposure. This strongly 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.

Tyrosine Kinase Inhibitors

There are currently 22 different TKIs marketed for the treatment of various cancer types. One of the key challenges with TKIs in the field of oncology involves the identification and pairing of the right patient with the right drug. However, even if the right drug is identified, important issues still remain regarding its optimal dose. Despite the revolutionary changes in the various stages of drug development used for TKIs (Humphrey et al., 2011), the standard strategy still in use for dose selection is to establish a therapeutic dose in phase II trials and subsequently, at best, modify it for individual differences in body surface area in children. This is an unsustainable situation since failure to deliver the right dose in routine practice may have detrimental implications for both the efficacy and safety of TKIs (Di Gion et al., 2011; Scheffler et al., 2011). Indeed, a wealth of clinical data have become available over the last few years indicating that clinical outcome, in particular decreased toxicity, can be optimized if dosing strategies for TKIs take into consideration their unique pharmacokinetic profiles. Moreover, although TKIs possibly offer a number of

important theoretical advantages over conventional cytotoxic chemotherapy, they are still afflicted by some of the same problems, including an extensive interindividual pharmacokinetic variability and the existence of a rather narrow therapeutic window (Baker and Hu, 2009). Although many of these targeting agents have been identified as substrates of various ATP-binding cassette protein transporters, the identity of SLCs that regulate absorption and disposition, as well as their uptake into tumor cells, remains essentially unknown.

Model-based simulations have indicated that a critical determinant of pharmacokinetic variability observed with TKIs is associated with absorption-related processes and to a lesser extent with clearance (Dai et al., 2008), and this has led to several studies exploring associations of intestinal SLCs with transport of TKIs. For example, the TKI imatinib has been identified as a substrate of OATP1A2 (SLCO1A2), OCTN1, and OCTN2, which are expressed in duodenal enterocytes (Glaeser et al., 2007; Hu et al., 2008), using heterologous expression models. Accordingly, investigators have reported preliminary results indicating that genetic variants in OATP1A2 are associated with altered pharmacokinetics of imatinib in cancer patients (Yamakawa et al., 2011) in a manner that is possibly dependent on racial ancestry (Eechoute et al., 2011). Recent reports have also been promising in regards to OCTN1 and OCTN2 in that genetic polymorphisms of these genes were associated with time to progression in patients with unresectable gastrointestinal stromal tumors treated with imatinib, as well as with a reduction in transcripts of the breakpoint cluster - Abelson (Bcr-Abl) fusion product (Angelini et al., 2013a,b), the main kinase target of imatinib.

There have been many studies claiming that OCT1 activity is associated with the accumulation of imatinib in leukemia cells and with responsiveness to treatment (Thomas et al., 2004; Crossman et al., 2005; Clark et al., 2008; Wang et al., 2008), although imatinib is a rather weak substrate of OCT1, and the causal connection of this transporter with the reported phenotypes remains uncertain (Hu et al., 2008; Wang et al., 2008). Nonetheless, since imatinib has high oral bioavailability and undergoes extensive hepatic metabolism, it is tempting to speculate that OCT1 is possibly involved in regulating hepatocellular entry of the drug. Since multiple TKIs, including imatinib, are transported substrates of OATP1B1 and/or OATP1B3 (Hu et al., 2008; Zimmerman et al., 2013), it is possible that multiple, potentially redundant SLCs are involved in the liver uptake process. Preliminary evidence supporting this thesis comes from a study in which genetic variation in OATP1B3 was shown to be linked with altered concentrations of imatinib in circulating cells as well as with altered oral clearance of the drug (Nambu et al., 2011). However, this same variant was not associated with response to treatment (Bedewy and El-Maghraby, 2013), and there is no evidence that this transporter is connected with imatinib-induced adverse events that would be either directly associated with uptake in a target tissue or indirectly through an effect on systemic drug levels.

Although clinically actionable data indicating that SLCs can regulate trafficking of TKIs and modulate toxicity or response remain lacking, some recent studies have revealed that TKIs can inhibit the activity of some transporters that are relevant to maintain homeostasis of natural endogenous substrates, via an off-target mechanism. For example, clinical safety profile investigations of pazopanib have determined that this drug causes an elevation in total bilirubin levels in patients without any evidence of direct liver damage. Since OATP1B1 is an important transporter that regulates levels of bilirubin (Johnson et al., 2009), the hyperbilirubinemia occurring in patients receiving pazopanib could be an artifact related to the TKI's inhibitory effects on OATP1B1 rather than represent liver injury (Xu et al., 2010). Another example of an interaction of endogenous SLC substrates with drugs is demonstrated by the ability of TKIs to inhibit OCT2, which facilitates transport of serum creatinine

into the renal tubule (Ciarimboli et al., 2012). Serum creatinine is used in routine practice to estimate glomerular filtration rate to assess kidney function, and since creatinine undergoes tubular secretion, this approach can overestimate glomerular filtration rate by as much as 20% (Breyer and Qi, 2010). Previous studies have indicated that competitive substrates of OCT2 can artificially increase serum creatinine, which could be mistakenly interpreted as evidence of renal injury (Dollery, 2013). A similar observation has been made with vandetanib, a TKI that markedly increases serum creatinine due to an inhibitory effect on OCT2-mediated transport of creatinine (Caprelsa prescribing information; see <http://www1.astrazeneca-us.com/pi/caprelsa.pdf>). The inhibition of OCT2 by vandetanib has also been proposed as a principle mechanism by which the TKI can increase the systemic exposure to cisplatin (Blackhall et al., 2010). Given that many TKIs can potentially inhibit OCT2 activity, this event is likely not restricted to vandetanib (Morrow et al., 2010; Minematsu and Giacomini, 2011). Moreover, vandetanib also potentially inhibits MATE1 and MATE2-K, further demonstrating that the function of multiple SLCs can be affected by off-target effects of this clinically important drug class (Shen et al., 2013).

Conclusion and Future of Field

The SLC transporters have an established role in regulating the pharmacokinetic profile of several oncology drugs, as well as in mediating the intrinsic cellular sensitivity of both healthy organs and malignant cells. Several polymorphic variants in SLC genes relevant to oncology drugs have been described in recent years, of which some, including those of the OATP1B-type transporter genes, may be of particular relevance to treatment outcome in patients with cancer. The actual *in vivo* effects of many SLCs in relation to their phenotypical consequences are still debatable, as contradictory results have been reported. Most studies published to date suffer from a lack of clinical evidence, or from small sample sizes in relation to the detected phenotypes *in vivo*, as well as from a host of potentially confounding factors that influence their outcome. Most important among these are environmental and physiologic factors that may affect expression or function of the SLCs, and confounding links to other genes or variants of putative relevance for drug absorption and/or disposition pathways. Additional research is clearly needed on the role of SLC in the handling of oncology drugs and how to use transporters to improve treatment by minimizing toxicity. However, considering the sheer magnitude of the number of SLCs identified thus far, it is evident that alternative strategies are required to identify additional, potentially important oncology drug-SLC pairs. Such future studies will hopefully clarify existing discrepant findings, and contribute to improving the quality of life and treatment outcome of a wide variety of malignant diseases.

Author Contributions

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