

# Current Understanding of Membrane Transporters as Regulators or Targets for Cisplatin-Induced Hearing Loss

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## ABSTRACT

Cisplatin is a platinum-based drug, which remains among the most efficacious anticancer treatment options. Unfortunately, use of cisplatin is hindered by dose-limiting toxicities, including irreversible hearing loss, which can grossly affect patient quality of life. Cisplatin-induced ototoxicity is the result of cochlear hair cell damage through a mechanism that is poorly understood. However, cisplatin cytotoxicity is reliant on intracellular accumulation, a process that is largely dependent on the presence of particular membrane transporters. This review will provide an update on our current understanding of the various transporters known to be involved in the disposition and cytotoxicity of platinum drugs or their metabolites, as well as their role in mediating cisplatin-induced hearing loss. We also provide a summary of the successes and opportunities in therapeutically targeting

membrane transporters to alleviate platinum-induced hearing loss. Moreover, we describe how this approach could be used to reduce the severity or onset of other adverse events associated with exposure to various forms of platinum drugs, without diminishing antitumor efficacy.

## SIGNIFICANCE STATEMENT

Cisplatin-induced hearing loss is a dose-limiting and irreversible adverse event with no current preventative or curative treatment measures. Pharmacological targeting of membrane transporters that regulate platinum uptake into cochlear hair cells, if conducted appropriately, may alleviate this devastating side effect and could be applied to alleviate other platinum-induced toxicities.

## Introduction

Cisplatin is considered among the most widely used therapeutics for various forms of cancer in children and adults. This is due to high efficacy in malignancies of tissues that include bladder, ovaries, testis, head and neck, and neuroblastoma (Rabik and Dolan, 2007; Harrach and Ciarimboli, 2015; Gold and Raja, 2020). Unfortunately, despite its widespread efficacy, cisplatin-based therapy is often limited by the onset of dose-restricting toxicities.

The major complications associated with cisplatin include neuro-, nephro-, and ototoxicity. These adverse events (AEs) are not only dose-limiting but also common, as nephrotoxicity affects 25%–33% of patients and nearly 70% suffer from ototoxicity (Madias and Harrington, 1978; Langer et al., 2013). Moreover, cisplatin-induced ototoxicity (CIO) is more debilitating

in children, at least 60% of whom experience permanent bilateral hearing loss (Langer et al., 2013). This can have devastating long-term impacts on quality of life and development, as impaired auditory function can impact communication, socialization, cognition, performance, and lifetime earnings (Gurney et al., 2007; Langer et al., 2013; Paken et al., 2016; Wilson et al., 2017). Unfortunately, despite uncovering remedies to mitigate nephrotoxicity (Crona et al., 2017), CIO is poorly understood, and there remains no applicable preventative or curative resolutions (Freyer et al., 2019, 2020).

Currently, it is understood that CIO is confined to the inner ear or cochlea, where inner-hair cells (IHCs) and outer-hair cells (OHCs), stria vascularis supporting cells, and spiral ganglion cells are affected (Paken et al., 2016). Collectively, these cells manage mechanotransduction required to perceive sound; however, cisplatin exposure promotes destruction of IHCs and OHCs. Details of factors regulating hair cell damage are limited, but cell death is attributed to platinum-DNA adduct formation (Basu and Krishnamurthy, 2010) or generation of reactive oxygen species, two attributes that also contribute to cisplatin antineoplastic effects (Bragado et al., 2007; Choi et al., 2015). As such, strategies to reduce CIO have sought to preserve hair cells by mitigating formation of DNA adducts or reactive oxygen species, although these approaches have not yielded clinical improvements. Meanwhile,

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**ABBREVIATIONS:** ABC, ATP-binding cassette; AE, adverse event; CIO, cisplatin-induced ototoxicity; CTR, copper transporter; IHC, inner-hair cell; MATE, multidrug and toxin extrusion protein; MCT, monocarboxylate transporter; OAT, organic anion transporter; OCT2, organic cation transporter 2; OHC, outer-hair cell; SLC, solute carrier; SNP, single nucleotide polymorphism.

cellular accumulation of cisplatin is largely dependent on specific membrane transporters, a characteristic that is considered understudied.

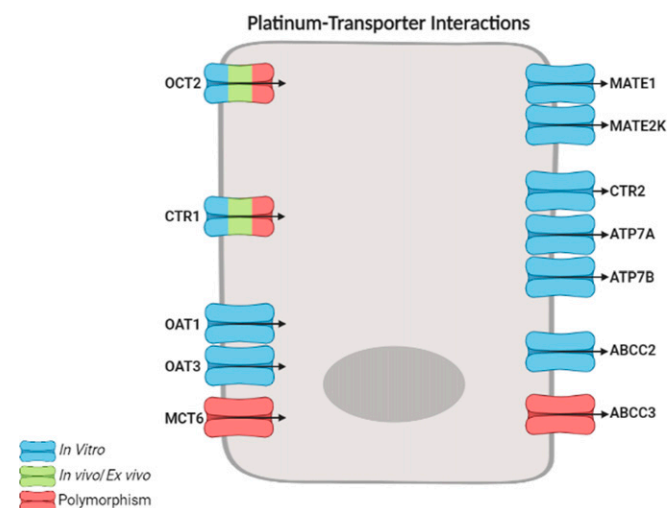
The human genome consists of more than 400 membrane transporters that are separated into two major superfamilies: the ATP-binding cassette (ABC) transporters, and solute carriers (SLC) (Borst and Elferink, 2002; He et al., 2009; Nigam, 2015). Collectively, these proteins are among the least studied family of proteins despite involvement in regulating cellular uptake or efflux of endogenous compounds and xenobiotics (Borst and Elferink, 2002; Nigam, 2015). The majority of membrane transporter investigations associated with xenobiotics focus on select proteins and their involvement of mediating drug absorption, distribution, metabolism, and excretion in organs such as the intestine, liver, kidney, and blood-brain barrier (Giacomini et al., 2010). However, all tissues express a variety of transporters, and knowledge of those responsible for cisplatin accumulation into hair cells would uncover key strategies to ameliorate CIO. This is especially advantageous in the event that cisplatin uptake into tumors is mediated by distinctively different transporters from those in hair cells. Furthermore, inhibition of transporters that mediate platinum disposition could be expanded to alleviate other platinum-based toxicities. For example, clinical use of oxaliplatin is often associated with peripheral neurotoxicity that worsens with higher cumulative doses into dorsal root ganglia (Grothey, 2005), and many patients exposed to carboplatin suffer from thrombocytopenia due to death of megakaryocytes (van der Vijgh, 1991; Markman et al., 2004). As mentioned above, cisplatin also promotes nephro- and neurotoxicity (van den Bent et al., 2002; de Jongh et al., 2003). Considering that each of these AEs develop as a result of cellular platinum accumulation, which is dependent on transport-mediated uptake, it is not a stretch to imagine targeting uptake transporters may have widely impactful benefits.

Over the past two decades, there has been literary expansion of transporters reportedly involved in platinum drug disposition and CIO, along with other forms of platinum-mediated toxicities.

## SLCs Involved in Cisplatin Disposition and CIO

Numerous SLCs have been reported to regulate cellular uptake of cisplatin (Fig. 1), serving as the primary step of cytotoxicity and as contributors to CIO. Below describes the transporters identified to date.

**Organic Cation Transporter 2 (SLC22A2).** OCT2 has been implicated as a promoter of tubular secretion and urinary elimination of cisplatin and oxaliplatin both *in vitro* and *in vivo* (Filipski et al., 2008; Filipski et al., 2009; Sprowl et al., 2013a), as well as oxaliplatin accumulation into rodent dorsal root ganglia (Sprowl et al., 2016). It is currently understood that the metabolically active, cationic form of cisplatin is transported into cells via OCT2 inciting cytotoxicity (Browning et al., 2017). Interestingly, OCT2 expression is highly tissue-specific, with the greatest found in proximal tubules (Filipski et al., 2009). OCT2 is also expressed in human and murine dorsal root ganglia (Sprowl et al., 2013a), as well as in IHC, OHC, and the stria vascularis of the cochlea in mice (Ciarimboli et al., 2010; More et al., 2010). In agreement with



**Fig. 1.** Transporters implicated in the disposition of cisplatin or its metabolites *in vitro* (blue) and *in vivo* or *ex vivo* (green). Relevant transporters with polymorphisms known to change cisplatin disposition, found from genome association studies, are also shown (red). A combination of the above colors means the transporter was found to interact with cisplatin across several experimental models, respective to their representative color. This image was created with BioRender online software.

tissue expression, several studies support the role of OCT2 in mediating CIO. Genetic deficiency of Oct2 in mice is protective of CIO (Ciarimboli et al., 2010; Sprowl et al., 2014), and rs316019 [Table 1; (c.808G>T; p.Ser270Ala)], a reduced functional OCT2 variant that exists within approximately 7%–13% of Caucasians (Filipski et al., 2008, 2009), has been associated with reduced incidence of CIO [Table 2; (Lanvers-Kaminsky, 2015)]. In contrast, one investigation was unable to confirm a protective role of rs316019 in patients [Table 2; (Drogemoller et al., 2017)], but a minor CIO protective effect of rs316019 was recently confirmed in a large patient population [Table 2; (Langer et al., 2020)]. These findings are encouraging, as cisplatin remains effective in xenograft or *in vitro* tumor models deficient of OCT2, indicating that pharmacological inhibition of this transporter has no impact on therapeutic efficacy (Ciarimboli et al., 2010; Ciarimboli, 2012; Sprowl et al., 2013b).

**Copper Transporters 1 and 2 (SLC31A1/2).** Consistent with its role in cellular uptake of heavy metals, *in vitro* overexpression of CTR1 increases cellular accumulation of cisplatin and consequential cytotoxicity (Holzer et al., 2004; Pabla et al., 2009). Similarly, CTR1 deficiency is associated with cisplatin resistance *in vitro* (Pabla et al., 2009; More et al., 2010). The role of CTR1 in managing cisplatin disposition and sensitivity is further strengthened by numerous *in vivo* and *ex vivo* studies. For example, genetic knockdown of CTR1 in mice diminishes platinum uptake into proximal and distal tubules and reduces the severity of cisplatin-induced nephrotoxicity (Pabla et al., 2009). CTR1 inhibition has also resulted in reduced cisplatin accumulation into isolated mouse cochlea (More et al., 2010). Clinical evidence also exists, as two reduced functional CTR1 variants in patients have been associated with cisplatin tumor resistance, whereas an increased functional variant is linked to more severe cisplatin-induced toxicity [Tables 1 and 2; (Xu et al.,

TABLE 1  
Transporter polymorphisms directly involved in cisplatin disposition and cisplatin-induced toxicities

Transporter	Identification	Substrate	Translation	Functional Change	Toxicity Change	Reference
OCT2	rs316019	Cationic, activated cisplatin	c.808T>G; p.Ser270 > Ala	Decreased	Decreased	Filipski et al., 2009
CTR1	rs12686377	Cationic, activated cisplatin	c.-35-14361C>A	Decreased	Decreased	Xu et al., 2012a
	rs7851395	Cationic, activated cisplatin	c.-35-15930A>G	Decreased	Decreased	Xu et al., 2012a
MCT6	rs10981694	Cationic, activated cisplatin	c.-36 + 2451T>G	Increased	Increased	Xu et al., 2012b
	rs4788863	Anionic NAC-1 metabolite	c.121T>C; p.Leu41 > Leu	Decreased	Decreased	Drogemoller et al., 2017
ABCC2	rs11597282	Anionic NAC-1 metabolite	n.-24C>T*	Decreased	Increased	Sun et al., 2010
ABCC3	rs1051640	Anionic NAC-1 metabolite	c.4509A>G; p.Glu1503 > Glu	Increased	Decreased	Pussegoda et al., 2013

2012a,b)]. As CTR1 is also expressed in IHCs, OHCs, and the stria vascularis of the cochlea of mice (More et al., 2010), a role for this transporter in mediating CIO is logical. However, CTR1 is widely expressed throughout human tissues, including various tumors (Ishida et al., 2010), implying that targeting this transporter pharmacologically to alleviate CIO could jeopardize antitumor efficacy.

In addition to CTR1, CTR2 has also been investigated as a regulator of cisplatin disposition. CTR2 is similar in homology and function to CTR1 but is associated with cellular efflux of cisplatin. Overexpression of CTR2 *in vitro* conveys cisplatin resistance, whereas decreased expression allows greater platinum accumulation and elevated cell death (Blair et al., 2009, 2011).

**Organic Anion Transporter 1 and 3 (SLC22A6/8).** The OAT1 and OAT3 transporters are highly specific to the basolateral membrane of kidney proximal tubules and were shown to contribute to cisplatin-induced renal toxicity *in vitro* (Nigam et al., 2015; Hu et al., 2017). These findings emerged after the observation that genetic deficiency of murine Oct2 provides only partial protection to cisplatin-induced nephrotoxicity *in vivo*. Meanwhile, OAT1 and OAT3 have been shown *in vitro* to mediate transport of the mercapturic acid cisplatin metabolite *N*-acetylcysteine S-conjugate (NAC-1), which is responsible for OCT2-independent cisplatin toxicity (Hu et al., 2017). NAC-1 is a powerful reducing agent with the propensity to interact with DNA (Townsend et al., 2003; Hu et al., 2017). This metabolite is also a precursor to a highly potent and reactive thiol molecule that can further elevate toxicity. Consistent with the above observations, Oat1 and Oat3 deficiency in mice is reportedly protective of nephrotoxicity, as determined by a noticeable reduction in blood urea nitrogen and serum creatinine after cisplatin exposure (Hu et al., 2017).

Recently, the involvement of OAT1 and OAT3 was challenged by Nieskens et al. (2018), who reported that cisplatin sensitivity was not increased in a proximal tubule cell line overexpressing OAT1 and OAT3, although the investigators did not assess cellular uptake or sensitivity to NAC-1, implying further investigation is warranted. Regardless, targeting OAT1 and OAT3 appears to be a viable approach considering that inhibition of these transporters does not compromise the efficacy of cisplatin *in vitro* (Hu et al., 2017). As such, the involvement of OAT1 and OAT3 in CIO and other cisplatin-induced AEs should be further explored.

**Monocarboxylate Transporter 6 (SLC16A5).** MCTs are generally well characterized, have broad tissue expression, and mediate the disposition of various drugs. However, less is

known about MCT6, a suspected orphan transporter. To date, no endogenous MCT6 substrates are known, but several xenobiotic substrates have been identified *in vitro* (Murakami et al., 2005; Fisel et al., 2018) and *in vivo* (Murakami et al., 2005; Fisel et al., 2018; Jones et al., 2020). Similar to other MCT family members, MCT6 is reportedly expressed across numerous tissues, including in the gut, kidney, and liver in humans. Interestingly, MCT6 protein expression has also been reported in murine cochlea (Drogemoller et al., 2017).

MCT6 has been implicated as a regulator of CIO since Drogemoller et al. (2017) identified a MCT6 single nucleotide polymorphism (SNP) in adult patients with testicular cancer that was associated with protection from hearing loss (Table 2). This particular variant, rs4788863 (c.121T>C; p.Leu41Leu), is predicted to be associated with lower mRNA expression and is expected to reduce cisplatin uptake and sensitivity (Table 1). Moreover, *in vitro* evidence demonstrates that cisplatin exposure appears to increase MCT6 mRNA expression; conversely small interfering RNA-mediated knockdown of MCT6 expression offers protection from cisplatin cytotoxicity, although only at lower concentrations (Drogemoller et al., 2017). Unfortunately, the genetic association of MCT6 and CIO has not been replicated in follow-up genome-wide association studies (Lui et al., 2018; Langer et al., 2020), implying that its true role requires focused investigation. This includes the mechanism by which MCT6 could contribute to platinum disposition, as cisplatin is not a prototypical substrate. In contrast, MCT6, recognized as an anion transporter, has substrate overlap with OATs and may be involved in disposition of cisplatin metabolites such as NAC-1 (Murakami et al., 2005; Fisel et al., 2018; Jones et al., 2020). To date, no literature exists demonstrating MCT6 expression in tumors, signifying that inhibition of MCT6 would likely not decrease antitumor efficacy; however, more research must be done to verify the absence of MCT6-dependent drug uptake across multiple tumor types.

## Efflux Transporters and Cisplatin Disposition

In addition to the SLCs described above, efflux transporters are also known to regulate cellular sensitivity to platinum drugs. The ABC transporters P-glycoprotein (ABCB1; Multidrug Resistant Protein1) and breast cancer resistant protein (ABCG2), which are commonly major suspects of clearing cytotoxic molecules from cells, do not recognize cisplatin (Yin et al., 2009; Wang et al., 2014; Vesel et al., 2017). However, other proteins have been identified as mediators of cisplatin efflux.

TABLE 2

Summary of existing clinical studies reporting on transporter-based treatments or variants

Transporter	Study	Outcome Measured	Number of PTs	Ages	Doses	Outcome
OCT2	Filipski et al. (2008)	rs316019 association with cisplatin nephrotoxicity	106	$y$ 18–75	$mg/m^2$ 50–100	rs316019 was identified and had no effect on cisplatin pharmacokinetics
	Drogemoller et al. (2017)	GWAS association with CIO	188	24–39	200–920	No retrospective involvement of rs316019 in CIO protection
	Langer et al., (2020)	SNP association with platinum toxicity	900	N/R	30–1650	rs316019 provides minor CIO protection but is a poor clinical marker in this model
CTR1	Xu et al., (2012a)	SNP association with platinum resistance	282	33–78	100	rs12686377 and rs7851395 decrease tumor efficacy of cisplatin
	Xu et al., (2012b)	SNP association with platinum toxicity and survival	204	33–77	100	rs10981694 is associated with increased severe CIO
MCT6	Drogemoller et al. (2017)	GWAS association with CIO	188	24–39	200–920	Retrospective analyses showed rs4788863 confers protection from CIO
	Langer et al. (2020)	SNPs association with platinum toxicity	900	N/R	30–1650	No association of rs4788863 with CIO
	Lui et al. (2018)	SNP association with CIO	106	0.2–16.9	N/R	No association of rs4788863 with CIO
ABCC2	Sun et al. (2010)	SNP association with overall survival	248	N/R	N/R	rs11597282 is associated with increased overall survival in SCLC patients
	Campa et al. (2012)	SNP association with overall survival and toxicity	377	N/R	N/R	rs11597282 associated with decreased efficacy and shorter overall survival in SCLC, but not NSCLC, patients
	Sprowl et al. (2012)	SNP association with cisplatin pharmacokinetics, efficacy, and toxicity	237	N/R	N/R	rs11597282 has no influence on nephrotoxicity, cisplatin response, or overall survival
ABCC3	Pussegoda et al. (2013)	SNPs as genetic markers for CIO	155	0–25	92–800	rs1051640, when integrated into a mathematical model, helped predict CIO
	Tserga et al. (2019)	Literature review of SNP association with CIO	N/R	N/R	N/R	rs1051640 is protective from CIO

N/R, not reported; PT, patient; SNP, single nucleotide polymorphism; GWAS, genome wide association study; SCLC, small-cell lung cancer; NSCLC, non-small-cell lung cancer.

**ATP7A and ATP7B.** Consistent with the role of CTR1, the copper efflux transporters ATP7A and ATP7B are reportedly involved in cisplatin sensitivity. The presence and/or upregulation of ATP7A/B transporters are associated with platinum-based tumor resistance both *in vitro* (Samimi et al., 2004) and *in vivo* (Samimi et al., 2004; Nakagawa et al., 2008). Similar to CTR1, ATP7A/B are widely expressed throughout human tissues, including the cochlea, where ATP7A is highly localized to pillar cells in the organ of Corti, and ATP7B is found in hair cells (Ding et al., 2011). Although ATP7A/B are hypothesized to play a role in CIO, no evidence exists to provide a direct association.

**Multidrug and Toxin Extrusion Protein 1 and 2K (SLC47A1/2).** MATE1 and MATE2K mediate the efflux of various cationic molecules, including numerous xenobiotics

(Nies et al., 2016). Cisplatin has been recognized as a substrate for both MATE1 and MATE2K in overexpressing cells (Sauzay et al., 2016), and MATE1 is classified as a protector against cisplatin-induced nephrotoxicity *in vivo* (Nakamura et al., 2010). Its role in renal efflux and protection of proximal tubules is not surprising considering that MATE1 is expressed among a variety of tissues, including the liver and kidney, whereas MATE2K is currently classified as kidney-specific. Neither MATE1 nor MATE2K expression has been reported in IHC or OHC, and as such, a contribution of MATE1 and MATE2K to CIO has not been discovered.

**Multidrug Resistance-Associated Protein 2 and 3 (ABCC2/3).** Unlike P-glycoprotein and breast cancer resistant protein, the ABCC-subfamily members ABCC2 and ABCC3, which are known glutathione conjugate transporters, reportedly

mediate efflux of cisplatin—or, more likely, cisplatin conjugates (Taniguchi et al., 1996; Cui et al., 1999; Chen and Kuo, 2010). More research is necessary to better define these interactions; however, ABCC2-overexpressing cells have greater tolerance to cisplatin as a result of increased cellular efflux *in vitro* (Kawabe et al., 1999), and genetic knockdown reverses cisplatin resistance in tumor cells (Chen et al., 2021). The role of ABCC2 is further strengthened by *in vivo* evidence, whereby ABCC2-deficient mice have greater renal and hepatic accumulation of platinum, along with increased nephrotoxicity, while reintroduction of human ABCC2 can remedy these events (Wen et al., 2014). These findings are consistent with ABCC2 expression that is largely localized to tissues associated with absorption or elimination, such as hepatic and gastrointestinal tissues, as well as renal proximal tubules (Jedlitschky et al., 2006). Furthermore, the discoveries in murine models are also consistent with human observations, in which the reduced functional ABCC2 variant rs11597282 [Table 1; (n.-24C>T)] has been associated with increased response to cisplatin and toxicity [Table 2; (Sun et al., 2010)]. However, this variant has also been reported to have no effect on cisplatin disposition or prognostic outcomes (e.g., progression free outcome, overall survival, and toxicity) in patients with different tumor types [Table 2; (Campa et al., 2012; Sprowl et al., 2012)], indicating that this particular variant warrants further study to clarify its role. This includes assessing a potential role in CIO, as there is currently no association of ABCC2 with this AE.

Although less is known about ABCC3 compared with the other ABCC-family members, this transporter has garnered recent interest in regulating cisplatin sensitivity. Several studies have postulated that rs1051640, an increased functional variant of ABCC3 [Table 1; (c.4509A>G; p.Glu1503Glu)] may provide protection from CIO [Table 2; (Pusegoda et al., 2013; Tserga et al., 2019)]. Unfortunately, its true clinical impact and the mechanism responsible remains unclear, as the involvement of ABCC3 in CIO is currently purely speculative. Furthermore, although ABCC3 is widely expressed throughout human tissues, expression has not yet been reported in cochlear cells.

### Clinical Outcome of Transporter-Targeting Strategies to Alleviate CIO

As described above, genetic variation of a few transporters involved in platinum disposition have been associated with clinical protection from CIO (Fig. 1; Table 1). These observations have sparked enthusiasm for strategies to manipulate transporter activity and reduce platinum accumulation into tissues linked with AEs. The challenge in alleviating CIO, however, is to regulate transporter function that limits cisplatin disposition into cochlear cells without sacrificing sufficient accumulation into tumors to maintain treatment efficacy. This has proven to be particularly challenging with efflux transporters implicated in cisplatin disposition, as there have been no pharmacological strategies to selectively target these proteins to prevent cisplatin-associated toxicities. In contrast, various investigations have been conducted to pharmacologically manipulate select SLCs involved in cisplatin uptake and CIO using *in vivo* and *ex vivo* models (Fig. 1).

Early attempts to alleviate CIO involved administering competitive inhibitors of CTR1 to restrict access into cochlear hair cells. *In vitro* and murine *ex vivo* evidence supports the utility of copper sulfate, a CTR1 substrate, to reduce

platinum accumulation and offer protection from cisplatin cytotoxicity (More et al., 2010). However, contradictory findings describing the limitations of copper sulfate to reduce CIO in *ex vivo* models have also been reported (Ding et al., 2011). Furthermore, this strategy is complicated by the widespread expression of CTR1 and its involvement in tumor uptake (More et al., 2010), as it is anticipated that application of copper sulfate or even copper chelators would simultaneously alter tumoral response. Ultimately, future studies would benefit from analyzing local application of CTR1 modulators.

In contrast to CTR1, tissue-specific expression of OCT2 provides a selective target to alleviate cisplatin-induced AEs without impacting clearance or efficacy in patients (Katsuda et al., 2010; Sprowl et al., 2013b). Multiple studies using *in vitro*, *ex vivo*, and *in vivo* models have reported that numerous OCT2 inhibitors, including cimetidine, pifithrin- $\alpha$ , and tyrosine kinase inhibitors alleviate cisplatin-mediated toxicities, including ototoxicity (Ciarimboli et al., 2005, 2010; Martins et al., 2013; Sprowl et al., 2013b, 2014). Unfortunately, clinical evidence of this approach to reduce CIO is limited. Lower incidence of CIO was observed in patients that were coadministered the OCT2 substrate erlotinib, although this was not the primary focus of the study (Martins et al., 2013). In contrast, pantoprazole did not offer protection from CIO, despite being administered as an OCT2 inhibitor (Fox et al., 2018). However, it is important to highlight that pantoprazole is reportedly a weak OCT2 inhibitor and would likely not provide CIO protection (Franke et al., 2010). Accordingly, the findings by Fox et al. (2018) may be irrelevant to this strategy, and future investigations need to include stronger candidate inhibitors.

In addition to use of potent transporter inhibitors, another ideal approach to provide maximum protection from CIO is to inhibit multiple transporters. As described above, loss of OCT2-mediated cisplatin accumulation into proximal tubules does not provide complete nephrotoxic protection but instead requires simultaneous inhibition of OAT1 and OAT3 to reduce NAC-1 uptake (Hu et al., 2017). In fact, probenecid reportedly inhibits uptake of NAC-1 by OAT1 and OAT3 *in vitro* and also provides protection from cisplatin-induced nephrotoxicity in patients (Jacobs et al., 1991; Hu et al., 2017). To date, however, NAC-1 and the transporters that mediate its disposition, including OAT1 and OAT3, have not been implicated in CIO. Furthermore, probenecid does not appear to offer protection from CIO (Jacobs et al., 1991). However, lack of protection from CIO may be the result of insufficient inhibition or involvement of other transporters. Regardless, accumulation of toxic metabolites or involvement of multiple transporters should be considered. Indeed, the otoprotective effect of cimetidine witnessed *in vivo* may involve its ability to simultaneously inhibit OCT2 and MCT6 (Murakami et al., 2005; Drogemoller et al., 2017). Therefore, clinical improvements would likely result from investigation of inhibitors targeting multiple transporters involved in cisplatin accumulation in IHCs and OHCs. For example, many tyrosine kinase inhibitors, such as erlotinib or nilotinib, may be attractive options given their ability to reduce the activity of multiple SLCs (Martins et al., 2013; Hu et al., 2017).

### Future Directions, Applications, and Considerations

This review highlights various studies that have collectively advanced our understanding of platinum disposition

and impact on CIO or other toxicities. However, the lack of clinical success stresses the need for further detailed investigations. Primarily, it is important to inspect the role of each transporter involved in platinum disposition, as there are likely additional transporters to be discovered. It is also particularly important to characterize the interplay of multiple transporters, as well as the involvement of metabolism, to identify all toxic platinum metabolites and the transporters that recognize these molecules. There is a high probability, based on the studies described above, that multiple transporters will need to be considered simultaneously to regulate platinum disposition and prevent accumulation into sensitive tissues. Strategies to target multiple transporters may carry significant risk, including altered homeostasis in tissues that express these proteins, or consequential reduced tumor uptake and efficacy. Clearly these events will require consideration throughout the development of such strategies; however, various investigations described above indicate that these risks may be minimal. For example, the competitive OCT2 inhibitor cimetidine is known to competitively inhibit multiple transporters and can be safely administered in patients without major risk of unintended effects in organs (Sprowl et al., 2013b). Moreover, *in vivo* data indicate that cimetidine has no effect on antitumor efficacy, which collectively suggests that certain transporter inhibitors can be used to selectively diminish toxicity without impacting tumor response.

Identification of ideal inhibitors is the most crucial task regarding the strategy to alleviate CIO by targeting transporters. Future inhibitors for clinical considerations must have well characterized properties regarding inhibition potential and success in alleviating CIO in preclinical models. The lack of success in ameliorating CIO with pantoprazole is not surprising considering that past literature reported mixed potential of this drug as an OCT2 inhibitor at clinically relevant doses (Franke et al., 2010; Nies et al., 2011; Hacker et al., 2015; Fox et al., 2018), and there was a lack of evidence showing that pantoprazole could prevent CIO *in vivo*. Instead, investigators should consider inhibitors that show promise at clinically relevant doses in reducing platinum-induced AEs within *in vitro* and *in vivo* models, such as cimetidine (Ciarimboli et al., 2010), or particular tyrosine kinase inhibitors (Bielefeld et al., 2013; Sprowl et al., 2016; Ateyya et al., 2017; Hu et al., 2017; Huang et al., 2020). Cyclin-dependent kinase inhibitors have also recently shown promise in alleviating platinum-induced toxicities *in vivo* through inhibition of transport (Pabla et al., 2015; Teitz et al., 2018) and could be further investigated. Additionally, as indicated above, ideal future inhibitors may also need to target multiple transporters, as long as tumor efficacy is unaffected. Unfortunately, because of expression across multiple tissues and decreased efficacy, inhibiting CTR1 or CTR2 is not recommended, as it is anticipated that a marked decrease in antitumor response or other off-site, unintended toxicities would occur. Manipulation of efflux transporters is also not recommended at this time because of their ubiquitous expression, difficulty in select targeting, and the potential to promote cellular accumulation of platinum agents. Currently, evidence suggests that OCT transporters would be optimal primary targets based on hair cell expression and involvement in cisplatin disposition; although simultaneous inhibition of particular anion uptake transporters

may provide more holistic protection from cisplatin toxicity. With this in mind, some tyrosine kinase inhibitors, such as nilotinib, are emerging as agents capable of reducing function of multiple transporters (Sprowl et al., 2016; Hu et al., 2017) and could be investigated as compounds to maximize protection from CIO. Although further work is needed to assure patient safety, the potential of using tyrosine kinase inhibitors in combination with cisplatin is supported by long-term use of tyrosine kinase inhibitors in the clinic and evidence of these drugs either having no impact or greater antitumor efficacy when given with cisplatin (Hu et al., 2017; Huang et al., 2020). In fact, use of tyrosine kinase inhibitors to ameliorate CIO is expected to only require a single dose before exposure to cisplatin and therefore may avoid AEs associated with this class of drugs (Hu et al., 2017; Huang et al., 2020). Finally, additional inhibitors could be identified or synthesized based on structure-activity explorations of known transporter substrates or inhibitors, which may yield improved clinical options.

Although optimal inhibitors will certainly advance clinical success of reducing CIO, it is also imperative to improve models that would accelerate translation to clinical application. For example, throughout cisplatin treatment, a consistent evaluative test of hearing loss associated with CIO needs to be established, as various methods and timing can yield differing sensitivity that could mask pharmacological benefits. Ideally, this common evaluative test would be applicable within *in vivo* models, which could then be used to test new strategies and accurately predict clinical success. Furthermore, the field would largely benefit from the generation of simulations with transporter modulators based on physiologically-based pharmacokinetic and pharmacodynamic mathematical modeling at clinically achievable concentrations to guide future research or strategies.

Although the current review focused widely on CIO, it is important to remember that numerous studies described above, in which transporters were investigated as mediators of platinum disposition, involved application to other forms of platinum-induced AEs. As such, the strategy of reducing platinum uptake into cells responsible for AEs can be applied to other platinum AEs as well. To date, there are no reports of successful clinical abolishment of platinum-induced nephrotoxicity, neuropathy, or thrombocytopenia. In fact, cimetidine has been the only transporter inhibitor administered to patients in combination with cisplatin, which was conducted in a study that revealed no risk of changes to cisplatin pharmacokinetics (Sprowl et al., 2013b). Although the study did not report on platinum-associated AEs, the lack of platinum pharmacokinetic changes, along with *in vivo* reports that have shown that targeting OCT2 can ameliorate cisplatin-induced nephrotoxicity, oxaliplatin-induced neurotoxicity, and CIO, is highly promising (Filipski et al., 2009; Sprowl et al., 2013a, 2016; Huang et al., 2020). Moreover, these findings have initiated a recent clinical trial to assess the potential of dasatinib to prevent oxaliplatin-induced neuropathy (Noonan et al., 2020). Certainly, the results of this clinical trial will highlight the feasibility of this strategy, however, data generated to date indicate that targeting select transporters can be beneficial to diminish all forms of platinum-induced AEs. Nonetheless, further study and clinical applications are required to assess the protective potential of this application to other platinum-induced AEs.

## Concluding Remarks

Because of its antitumor efficacy (Brown et al., 2019), cisplatin is likely to remain the standard of care for various cancers throughout the foreseeable future. As cancer rates rise (Ferlay et al., 2015), this means that quality of life—altering AEs, such as CIO, will become increasingly burdensome. Although strategies to abolish CIO through targeting cytotoxic properties are attractive, there remains high risk of reducing antitumor activity. However, evidence indicates that various membrane transporters—some highly tissue-specific—mediate platinum disposition and could be pharmacologically regulated to selectively reduce CIO without sacrificing antitumor efficacy. Despite success using *in vitro* and *in vivo* models, current approaches have not been adequately expanded to yield ideal clinical benefits.

Yet, the success of *in vitro*, *ex vivo*, and *in vivo* investigations indicates that regulating transporter function is a viable approach to mitigate platinum-induced AEs, including CIO. Clearly, though, additional research is needed to unveil the true benefits or potential detriments of transporter-based strategies to alleviate CIO or other forms of toxicity. However, given the complications, as well as the emotional and financial burden of CIO and other platinum-induced AEs, future studies and strategies to control platinum disposition should be expanded clinically, as regulation of these events will improve quality of life and treatment success by alleviating major dose-limiting AEs.

### Authorship Contributions

Wrote or contributed to the writing of the manuscript: Pasquariello, Dey, Sprowl.

### References

- Ateyya H, Hassan ZA, and El-Sherbeeny NA (2017) The selective tyrosine kinase-inhibitor nilotinib alleviates experimentally induced cisplatin nephrotoxicity and hepatotoxicity. *Environ Toxicol Pharmacol* **55**:60–67.
- Basu A and Krishnamurthy S (2010) Cellular responses to Cisplatin-induced DNA damage. *J Nucleic Acids* **2010**:201367.
- Bielefeld EC, Tanaka C, Chen GD, Coling D, Li M, Henderson D, and Fetoni AR (2013) An Src-protein tyrosine kinase inhibitor to reduce cisplatin ototoxicity while preserving its antitumor effect. *Anticancer Drugs* **24**:43–51.
- Blair BG, Larson CA, Adams PL, Abada PB, Pesce CE, Safaei R, and Howell SB (2011) Copper transporter 2 regulates endocytosis and controls tumor growth and sensitivity to cisplatin *in vivo*. *Mol Pharmacol* **79**:157–166.
- Blair BG, Larson CA, Safaei R, and Howell SB (2009) Copper transporter 2 regulates the cellular accumulation and cytotoxicity of Cisplatin and Carboplatin. *Clin Cancer Res* **15**:4312–4321.
- Borst P and Elferink RO (2002) Mammalian ABC transporters in health and disease. *Annu Rev Biochem* **71**:537–592.
- Bragado P, Armesilla A, Silva A, and Porras A (2007) Apoptosis by cisplatin requires p53 mediated p38alpha MAPK activation through ROS generation. *Apoptosis* **12**:1733–1742.
- Brown A, Kumar S, and Tchounwou PB (2019) Cisplatin-based chemotherapy of human cancers. *J Cancer Sci Ther* **11**:97.
- Browning RJ, Reardon PJT, Parhizkar M, Pedley RB, Edirisinghe M, Knowles JC, and Stride E (2017) Drug delivery strategies for platinum-based chemotherapy. *ACS Nano* **11**:8560–8578.
- Campa D, Müller P, Edler L, Knoefel L, Barale R, Heussel CP, Thomas M, Canzian F, and Risch A (2012) A comprehensive study of polymorphisms in ABCB1, ABCG2 and ABCG2 and lung cancer chemotherapy response and prognosis. *Int J Cancer* **131**:2920–2928.
- Chen HH and Kuo MT (2010) Role of glutathione in the regulation of Cisplatin resistance in cancer chemotherapy. *Met Based Drugs* **2010**:430939.
- Chen Y, Zhou H, Yang S, and Su D (2021) Increased ABCC2 expression predicts cisplatin resistance in non-small cell lung cancer. *Cell Biochem Funct* **39**:277–286.
- Choi YM, Kim HK, Shim W, Anwar MA, Kwon JW, Kwon HK, Kim HJ, Jeong H, Kim HM, Hwang D, et al. (2015) Mechanism of cisplatin-induced cytotoxicity is correlated to impaired metabolism due to mitochondrial ROS generation. *PLoS One* **10**:e0135083.
- Ciarimboli G (2012) Membrane transporters as mediators of Cisplatin effects and side effects. *Scientifica (Cairo)* **2012**:473829.
- Ciarimboli G, Deuster D, Knief A, Sperling M, Holtkamp M, Edemir B, Pavenstädt H, Lanvers-Kaminsky C, am Zehnhoff-Dinnesen A, Schinkel AH, et al. (2010) Organic cation transporter 2 mediates cisplatin-induced oto- and nephrotoxicity and is a target for protective interventions. *Am J Pathol* **176**:1169–1180.
- Ciarimboli G, Ludwig T, Lang D, Pavenstädt H, Koepsell H, Piechota HJ, Haier J, Jaehde U, Zisowsky J, and Schlatter E (2005) Cisplatin nephrotoxicity is critically mediated via the human organic cation transporter 2. *Am J Pathol* **167**:1477–1484.
- Crona DJ, Faso A, Nishijima TF, McGraw KA, Galsky MD, and Milowsky MI (2017) A systematic review of strategies to prevent cisplatin-induced nephrotoxicity. *Oncologist* **22**:609–619.
- Cui Y, König J, Buchholz JK, Spring H, Leier I, and Keppler D (1999) Drug resistance and ATP-dependent conjugate transport mediated by the apical multidrug resistance protein, MRP2, permanently expressed in human and canine cells. *Mol Pharmacol* **55**:929–937.
- de Jongh FE, van Veen RN, Veltman SJ, de Wit R, van der Burg ME, van den Bent MJ, Planting AS, Graveland WJ, Stoter G, and Verweij J (2003) Weekly high-dose cisplatin is a feasible treatment option: analysis on prognostic factors for toxicity in 400 patients. *Br J Cancer* **88**:1199–1206.
- Ding D, He J, Allman BL, Yu D, Jiang H, Seigel GM, and Salvi RJ (2011) Cisplatin ototoxicity in rat cochlear organotypic cultures. *Hear Res* **282**:196–203.
- Drögemöller BI, Monzon JG, Bhavsar AP, Borrie AE, Brooks B, Wright GEB, Liu G, Renouf DJ, Kollmannsberger CK, Bedard PL, et al. (2017) Association between SLC16A5 genetic variation and cisplatin-induced ototoxic effects in adult patients with testicular cancer. *JAMA Oncol* **3**:1558–1562.
- Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, and Bray F (2015) Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* **136**:E359–E386.
- Filipski KK, Loos WJ, Verweij J, and Sparreboom A (2008) Interaction of Cisplatin with the human organic cation transporter 2. *Clin Cancer Res* **14**:3875–3880.
- Filipski KK, Mathijssen RH, Mikkelsen TS, Schinkel AH, and Sparreboom A (2009) Contribution of organic cation transporter 2 (OCT2) to cisplatin-induced nephrotoxicity. *Clin Pharmacol Ther* **86**:396–402.
- Fisel P, Schaeffeler E, and Schwab M (2018) Clinical and functional relevance of the monocarboxylate transporter family in disease pathophysiology and drug therapy. *Clin Transl Sci* **11**:352–364.
- Fox E, Levin K, Zhu Y, Segers B, Balamuth N, Womer R, Bagatell R, and Balis F (2018) Pantoprazole, an inhibitor of the organic cation transporter 2, does not ameliorate cisplatin-related ototoxicity or nephrotoxicity in children and adolescents with newly diagnosed osteosarcoma treated with methotrexate, doxorubicin, and cisplatin. *Oncologist* **23**:762–e79.
- Franke RM, Kosloske AM, Lancaster CS, Filipiński KK, Hu C, Zolk O, Mathijssen RH, and Sparreboom A (2010) Influence of Oct1/Oct2-deficiency on cisplatin-induced changes in urinary N-acetyl-beta-D-glucosaminidase. *Clin Cancer Res* **16**:4198–4206.
- Freyer DR, Brock P, Knight K, Reaman G, Cabral S, Robinson PD, and Sung L (2019) Interventions for cisplatin-induced hearing loss in children and adolescents with cancer. *Lancet Child Adolesc Health* **3**:578–584.
- Freyer DR, Brock PR, Chang KW, Dupuis LL, Epelman S, Knight K, Mills D, Phillips R, Potter E, Risby D, et al. (2020) Prevention of cisplatin-induced ototoxicity in children and adolescents with cancer: a clinical practice guideline. *Lancet Child Adolesc Health* **4**:141–150.
- Giacomini KM, Huang SM, Tweedie DJ, Benet LZ, Brouwer KL, Chu X, Dahlin A, Evers R, Fischer V, Hillgren KM, et al.; International Transporter Consortium (2010) Membrane transporters in drug development. *Nat Rev Drug Discov* **9**:215–236.
- Gold JM and Raja A (2020) Cisplatin (Cisplatinum). StatPearls, Treasure Island, FL.
- Grothey A (2005) Clinical management of oxaliplatin-associated neurotoxicity. *Clin Colorectal Cancer* **5** (Suppl 1):S38–S46.
- Gurney JG, Tersak JM, Ness KK, Landler W, Matthay KK, and Schmidt ML; Children's Oncology Group (2007) Hearing loss, quality of life, and academic problems in long-term neuroblastoma survivors: a report from the Children's Oncology Group. *Pediatrics* **120**:e1229–e1236.
- Hacker K, Maas R, Kornhuber J, Fromm MF, and Zolk O (2015) Substrate-dependent inhibition of the human organic cation transporter OCT2: a comparison of metformin with experimental substrates. *PLoS One* **10**:e0136451.
- Harrach S and Ciarimboli G (2015) Role of transporters in the distribution of platinum-based drugs. *Front Pharmacol* **6**:85.
- He L, Vasilidou K, and Nebert DW (2009) Analysis and update of the human solute carrier (SLC) gene superfamily. *Hum Genomics* **3**:195–206.
- Holzer AK, Samimi G, Katano K, Naerdemann W, Lin X, Safaei R, and Howell SB (2004) The copper influx transporter human copper transport protein 1 regulates the uptake of cisplatin in human ovarian carcinoma cells. *Mol Pharmacol* **66**:817–823.
- Hu S, Leblanc AF, Gibson AA, Hong KW, Kim JY, Janke LJ, Li L, Vasilyeva A, Finkelstein DB, Sprowl JA, et al. (2017) Identification of OAT1/OAT3 as contributors to cisplatin toxicity. *Clin Transl Sci* **10**:412–420.
- Huang KM, Leblanc AF, Uddin ME, Kim JY, Chen M, Eisenmann ED, Gibson AA, Li Y, Hong KW, DiGiacomo D, et al. (2020) Neuronal uptake transporters contribute to oxaliplatin neurotoxicity in mice. *J Clin Invest* **130**:4601–4606.
- Ishida S, McCormick F, Smith-McCune K, and Hanahan D (2010) Enhancing tumor-specific uptake of the anticancer drug cisplatin with a copper chelator. *Cancer Cell* **17**:574–583.
- Jacobs C, Kaubisch S, Halsey J, Lum BL, Gosland M, Coleman CN, and Sikic BI (1991) The use of probenecid as a chemoprotector against cisplatin nephrotoxicity. *Cancer* **67**:1518–1524.
- Jedlitschky G, Hoffmann U, and Kroemer HK (2006) Structure and function of the MRP2 (ABCC2) protein and its role in drug disposition. *Expert Opin Drug Metab Toxicol* **2**:351–366.
- Jones RS, Parker MD, and Morris ME (2020) Monocarboxylate transporter 6-mediated interactions with prostaglandin F<sub>2α</sub>: *in vivo* and *in vivo* evidence utilizing a knockout mouse model. *Pharmaceutics* **12**:E201.

- Katsuda H, Yamashita M, Katsura H, Yu J, Waki Y, Nagata N, Sai Y, and Miyamoto K (2010) Protecting cisplatin-induced nephrotoxicity with cimetidine does not affect antitumor activity. *Biol Pharm Bull* **33**:1867–1871.
- Kawabe T, Chen ZS, Wada M, Uchiyama T, Ono M, Akiyama S, and Kuwano M (1999) Enhanced transport of anticancer agents and leukotriene C4 by the human canalicular multispecific organic anion transporter (cMOAT/MRP2). *FEBS Lett* **456**:327–331.
- Langer T, am Zehnhoff-Dinnesen A, Radtke S, Meitert J, and Zolk O (2013) Understanding platinum-induced ototoxicity. *Trends Pharmacol Sci* **34**:458–469.
- Langer T, Clemens E, Broer L, Maier L, Uitterlinden AG, de Vries ACH, van Grotel M, Pluijm SFM, Binder H, Mayer B, et al.; PanCareLIFE consortium (2020) Usefulness of current candidate genetic markers to identify childhood cancer patients at risk for platinum-induced ototoxicity: results of the European PanCareLIFE cohort study. *Eur J Cancer* **138**:212–224.
- Lui G, Bouazza N, Denoyelle F, Moine M, Brugières L, Chastagner P, Corradini N, Entz-Werle N, Vêrité C, Landmanparker J, et al. (2018) Association between genetic polymorphisms and platinum-induced ototoxicity in children. *Oncotarget* **9**:30883–30893.
- Madias NE and Harrington JT (1978) Platinum nephrotoxicity. *Am J Med* **65**:307–314.
- Markman M, Markman J, Webster K, Zanotti K, Kulp B, Peterson G, and Belinson J (2004) Thrombocytopenia associated with second-line carboplatin-based chemotherapy for ovarian, fallopian tube, and primary peritoneal cavity cancers. *J Cancer Res Clin Oncol* **130**:741–744.
- Martins RG, Parvathaneni U, Bauman JE, Sharma AK, Razez LE, Papagikos MA, Yunus F, Kurland BF, Eaton KD, Liao JJ, et al. (2013) Cisplatin and radiotherapy with or without erlotinib in locally advanced squamous cell carcinoma of the head and neck: a randomized phase II trial. *J Clin Oncol* **31**:1415–1421.
- More SS, Akil O, Ianculescu AG, Geier EG, Lustig LR, and Giacomini KM (2010) Role of the copper transporter, CTR1, in platinum-induced ototoxicity. *J Neurosci* **30**:9500–9509.
- Murakami Y, Kohyama N, Kobayashi Y, Ohbayashi M, Ohtani H, Sawada Y, and Yamamoto T (2005) Functional characterization of human monocarboxylate transporter 6 (SLC16A5). *Drug Metab Dispos* **33**:1845–1851.
- Nakagawa T, Inoue Y, Kodama H, Yamazaki H, Kawai K, Suemizu H, Masuda R, Iwazaki M, Yamada S, Ueyama Y, et al. (2008) Expression of copper-transporting P-type adenosine triphosphatase (ATP7B) correlates with cisplatin resistance in human non-small cell lung cancer xenografts. *Oncol Rep* **20**:265–270.
- Nakamura T, Yonezawa A, Hashimoto S, Katsura T, and Inui K (2010) Disruption of multidrug and toxin extrusion MATE1 potentiates cisplatin-induced nephrotoxicity. *Biochem Pharmacol* **80**:1762–1767.
- Nies AT, Damme K, Kruck S, Schaeffeler E, and Schwab M (2016) Structure and function of multidrug and toxin extrusion proteins (MATEs) and their relevance to drug therapy and personalized medicine. *Arch Toxicol* **90**:1555–1584.
- Nies AT, Hofmann U, Resch C, Schaeffeler E, Rius M, and Schwab M (2011) Proton pump inhibitors inhibit metformin uptake by organic cation transporters (OCTs). *PLoS One* **6**:e22163.
- Nieskens TTG, Peters JGP, Dabaghie D, Korte D, Jansen K, Van Asbeck AH, Tavraz NN, Friedrich T, Russel FGM, Masereeuw R, et al. (2018) Expression of organic anion transporter 1 or 3 in human kidney proximal tubule cells reduces cisplatin sensitivity. *Drug Metab Dispos* **46**:592–599.
- Nigam SK (2015) What do drug transporters really do? *Nat Rev Drug Discov* **14**:29–44.
- Nigam SK, Wu W, Bush KT, Hoening MP, Blantz RC, and Bhatnagar V (2015) Handling of drugs, metabolites, and uremic toxins by kidney proximal tubule drug transporters. *Clin J Am Soc Nephrol* **10**:2039–2049.
- Noonan AM, Lustberg MB, Schnell P, Hays JL, Jin N, Abushahin LI, Malalur PG, Roychowdhury S, Elkhatib RT, Chen H, et al. (2020) A phase Ib adaptive study of dasatinib for the prevention of oxaliplatin-induced neuropathy in patients with metastatic colorectal cancer receiving FOLFOX chemotherapy and bevacizumab. *J Clin Oncol* **38**.
- Pabla N, Gibson AA, Buege M, Ong SS, Li L, Hu S, Du G, Sprowl JA, Vasilyeva A, Janke LJ, et al. (2015) Mitigation of acute kidney injury by cell-cycle inhibitors that suppress both CDK4/6 and OCT2 functions. *Proc Natl Acad Sci USA* **112**:5231–5236.
- Pabla N, Murphy RF, Liu K, and Dong Z (2009) The copper transporter Ctr1 contributes to cisplatin uptake by renal tubular cells during cisplatin nephrotoxicity. *Am J Physiol Renal Physiol* **296**:F505–F511.
- Paken J, Govender CD, Pillay M, and Sewram V (2016) Cisplatin-associated ototoxicity: a review for the health professional. *J Toxicol* **2016**:1809394.
- Pusseghoda K, Ross CJ, Visscher H, Yazdanpanah M, Brooks B, Rassekh SR, Zada YF, Dubé MP, Carleton BC, and Hayden MR; CPNDS Consortium (2013) Replication of TPMT and ABCB3 genetic variants highly associated with cisplatin-induced hearing loss in children. *Clin Pharmacol Ther* **94**:243–251.
- Rabik CA and Dolan ME (2007) Molecular mechanisms of resistance and toxicity associated with platinating agents. *Cancer Treat Rev* **33**:9–23.
- Samimi G, Katano K, Holzer AK, Safaei R, and Howell SB (2004) Modulation of the cellular pharmacology of cisplatin and its analogs by the copper exporters ATP7A and ATP7B. *Mol Pharmacol* **66**:25–32.
- Sauzay C, White-Koning M, Hennebelle I, Deluche T, Delmas C, Imbs DC, Chatelut E, and Thomas F (2016) Inhibition of OCT2, MATE1 and MATE2-K as a possible mechanism of drug interaction between pazopanib and cisplatin. *Pharmacol Res* **110**:89–95.
- Sprowl JA, Ciarimboli G, Lancaster CS, Giovinazzo H, Gibson AA, Du G, Janke LJ, Cavaletti G, Shields AF, and Sparreboom A (2013a) Oxaliplatin-induced neurotoxicity is dependent on the organic cation transporter OCT2. *Proc Natl Acad Sci USA* **110**:11199–11204.
- Sprowl JA, Gregorc V, Lazzari C, Mathijssen RH, Loos WJ, and Sparreboom A (2012) Associations between ABCB2 polymorphisms and cisplatin disposition and efficacy. *Clin Pharmacol Ther* **91**:1022–1026.
- Sprowl JA, Lancaster CS, Pabla N, Hermann E, Kosloske AM, Gibson AA, Li L, Zeeh D, Schlatter E, Janke LJ, et al. (2014) Cisplatin-induced renal injury is independently mediated by OCT2 and p53. *Clin Cancer Res* **20**:4026–4035.
- Sprowl JA, Ong SS, Gibson AA, Hu S, Du G, Lin W, Li L, Bharill S, Ness RA, Stecula A, et al. (2016) A phosphotyrosine switch regulates organic cation transporters. *Nat Commun* **7**:10880.
- Sprowl JA, van Doorn L, Hu S, van Gerven L, de Bruijn P, Li L, Gibson AA, Mathijssen RH, and Sparreboom A (2013b) Conjointive therapy of cisplatin with the OCT2 inhibitor cimetidine: influence on antitumor efficacy and systemic clearance. *Clin Pharmacol Ther* **94**:585–592.
- Sun Z, Chen J, Aakre J, Marks RS, Garces YY, Jiang R, Idowu O, Cunningham JM, Liu Y, Pankratz VS, et al. (2010) Genetic variation in glutathione metabolism and DNA repair genes predicts survival of small-cell lung cancer patients. *Ann Oncol* **21**:2011–2016.
- Taniguchi K, Wada M, Kohno K, Nakamura T, Kawabe T, Kawakami M, Kagotani K, Okumura K, Akiyama S, and Kuwano M (1996) A human canalicular multispecific organic anion transporter (cMOAT) gene is overexpressed in cisplatin-resistant human cancer cell lines with decreased drug accumulation. *Cancer Res* **56**:4124–4129.
- Teitz T, Fang J, Goktug AN, Bonga JD, Diao S, Hazlitt RA, Iconaru L, Morfouace M, Currier D, Zhou Y, et al. (2018) CDK2 inhibitors as candidate therapeutics for cisplatin- and noise-induced hearing loss. *J Exp Med* **215**:1187–1203.
- Townsend DM, Marto JA, Deng M, Macdonald TJ, and Hanigan MH (2003) High pressure liquid chromatography and mass spectrometry characterization of the nephrotoxic biotransformation products of Cisplatin. *Drug Metab Dispos* **31**:705–713.
- Tserga E, Nandwani T, Edvall NK, Bulla J, Patel P, Canlon B, Cederoth CR, and Baguley DM (2019) The genetic vulnerability to cisplatin ototoxicity: a systematic review. *Sci Rep* **9**:3455.
- van den Bent MJ, van Putten WL, Hilken PH, de Wit R, and van der Burg ME (2002) Retreatment with dose-dense weekly cisplatin after previous cisplatin chemotherapy is not complicated by significant neuro-toxicity. *Eur J Cancer* **38**:387–391.
- van der Vijgh WJ (1991) Clinical pharmacokinetics of carboplatin. *Clin Pharmacokinet* **21**:242–261.
- Vesel M, Rapp J, Feller D, Kiss E, Jaromi L, Meggyes M, Miskei G, Duga B, Smuk G, Laszlo T, et al. (2017) ABCB1 and ABCG2 drug transporters are differentially expressed in non-small cell lung cancers (NSCLC) and expression is modified by cisplatin treatment via altered Wnt signaling. *Respir Res* **18**:52.
- Wang XK, To KK, Huang LY, Xu JH, Yang K, Wang F, Huang ZC, Ye S, and Fu LW (2014) Afatinib circumvents multidrug resistance via dually inhibiting ATP binding cassette subfamily G member 2 *in vitro* and *in vivo*. *Oncotarget* **5**:11971–11985.
- Wen X, Buckley B, McCandlish E, Goedken MJ, Syed S, Pelis R, Manautou JE, and Aleksunes LM (2014) Transgenic expression of the human MRP2 transporter reduces cisplatin accumulation and nephrotoxicity in MRP2-null mice. *Am J Pathol* **184**:1299–1308.
- Wilson BS, Tucci DL, Merson MH, and O'Donoghue GM (2017) Global hearing health care: new findings and perspectives. *Lancet* **390**:2503–2515.
- Xu X, Duan L, Zhou B, Ma R, Zhou H, and Liu Z (2012a) Genetic polymorphism of copper transporter protein 1 is related to platinum resistance in Chinese non-small cell lung carcinoma patients. *Clin Exp Pharmacol Physiol* **39**:786–792.
- Xu X, Ren H, Zhou B, Zhao Y, Yuan R, Ma R, Zhou H, and Liu Z (2012b) Prediction of copper transport protein 1 (CTR1) genotype on severe cisplatin induced toxicity in non-small cell lung cancer (NSCLC) patients. *Lung Cancer* **77**:438–442.
- Yin JY, Huang Q, Yang Y, Zhang JT, Zhong MZ, Zhou HH, and Liu ZQ (2009) Characterization and analyses of multidrug resistance-associated protein 1 (MRP1/ABCC1) polymorphisms in Chinese population. *Pharmacogenet Genomics* **19**:206–216.

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