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Hepatobiliary transporters in the pharmacology and toxicology of anticancer drugs

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1. ABSTRACT

The existence of carrier proteins located in the basolateral and apical membranes of hepatocytes, cholangiocytes and epithelial cells of the ileal mucosa, together with their more or less broad substrate specificities -implying their ability to transport many different drugs, including anticancer drugs- has important pharmacological repercussions. These vary from the existence of interactions of drugs with endogenous and xenobiotic substances to the possibility of using these transporters in the targeting of drug delivery systems, which can be useful either to direct anticancer drugs towards tumors located in the hepatobiliary system or to facilitate their hepatobiliary excretion. This justifies the growing interest in bile acid derivatives as targeted pharmacological tools, in general, and in anticancer chemotherapy, in particular. Moreover, interactions of antitumor drugs with hepatobiliary transporters may account for the appearance of toxic side effects associated with the use of these drugs. The present review covers these aspects of the pharmacology and toxicology of hepatobiliary transport systems in relation to anticancer drugs.

2. INTRODUCTION

The elimination of drugs by the liver is the result of a series of complex events that include uptake across the sinusoidal membrane of hepatocytes (phase 0 of the detoxification process). In some cases, this is followed by intracellular biotransformation, either by oxidoreduction reactions (phase I), or conjugation with polyatomic groups (phase II). Phase III processes involve the extrusion of native or biotransformed compounds across the canalicular membrane into the bile (phase IIIa) or, alternatively, across the sinusoidal membrane back into the blood (phase IIIb), which, for instance in cholestasis, may become a major pathway for exporting towards the kidney compounds that must be detoxified and eliminated from the body.

3. HEPATOBILIARY TRANSPORT OF ANTICANCER DRUGS

In the liver, phase 0 is accounted for by sodium-independent transporters of organic anions and cations as well as by very efficient sodium-dependent systems.

Table 1. Carriers involved in the uptake and export of anticancer drugs by parenchymal liver cells

Group	Typical compounds	Action mechanism	Uptake Carrier (Reference)	Export Pump (Reference)
Nitrogen mustards	Chlorambucil Melphalan	Alkylating agents	SLC7A5 (Melphalan; 55,56,57)	MRP1 (101) MRP2 (Chlorambucil; 93)
Oxazaphosphorines	Cyclophosphamide Ifosfamide	Alkylating agents		BCRP, MRP1, MRP2, MRP4 (94)
Acyclic nucleoside phosphonates	Adefovir Cidofovir	Antimetabolites	OAT1 (32)	MRP4 (105) MRP8 (117)
Pteridines	Methotrexate	Antimetabolites	OATP1A2 (7) OATP1B3 (8) OAT2 (25) OAT1, OAT3, OAT4 (28)	MDR1 (71) MRP1, MRP2 (95) MRP3 (109) MRP4 (107) MRP8 (115) BCRP (130,131)
Purine-base analogs	6-Mercaptopurine Thioguanine	Antimetabolites	OAT3 (31) CNT3 (46) ENT2 (46,47)	MDR1 (72) MRP4 (106) MRP5 (110)
Pyrimidine-base analogs	Fluorouracil Gemcitabine	Antimetabolites	OAT2 (Fluorouracil; 29) CNT1, ENT1, ENT2 (Gemcitabine; 48, 49, 50)	MRP8 (116)
Urea derivatives	Hydroxyurea	Antimetabolites	Oatp1a4 (12)	
Taxoids	Paclitaxel	Antimitotic agents	OAT2 (29) OATP1B3 (10,11)	MDR1 (73) MDR3 (84) MRP7 (114)
Vinca alkaloids	Vincristine Vinblastine	Antimitotic agents		MDR1 (68) MDR3 (84) mBsep (88) MRP1 (104) MRP2 (96) MRP7 (114)
Platinum compounds	Cisplatin Oxaliplatin	Cross-linking reagents	CTR1 (Cisplatin; 52,53) OCT1 (Oxaliplatin; 36) OCT2 (Cisplatin; 38)	MRP2 (97) MRP6 (113)
Flavonoids	Flavopiridol	Cyclin-dependent kinase inhibitors		BCRP (132)
Stilbenes	Tamoxifen	Estrogen receptor modulators	OATs (Raloxifene; 30)	MDR1 (74) MRP2 (30) BCRP (133)
Glycopeptide antibiotics	Bleomycin	DNA-damaging agents	Polyamine transport system in yeast (39) Its ortholog in humans is probably OCT1 (40)	
Aminoacridines	Amsacrine	Intercalating agents		MDR1 (75)
Anthracenyl hydrazones	Bisantrene	Intercalating agents		MDR1 (76) BCRP (121)
Anthracyclines	Doxorubicin	Intercalating agents	SLC22A16 (42) Non carrier-mediated (58, 59)	ABCA8 (62) MDR1 (66) MRP1 (104) MRP2 (97) MRP6 (113) BCRP (123,134)
Anthraquinones	Mitoxantrone	Intercalating agents	OCT1 (33) Non carrier-mediated (59)	MDR1 (75) MRP1 (102) BCRP (123,134)
Camptothecin analogs	Irinotecan Topotecan	Topoisomerase I inhibitors	OATP1B1 (Irinotecan; 9)	MDR1 (77) MRP1 (103) MRP2 (98) MRP4 (108) BCRP (135,136)
Podophyllotoxins	Etoposide Teniposide	Topoisomerase II inhibitors		MDR1 (68) MRP1 (104) MRP2 (97) MRP3 (109) MRP6 (113) BCRP (137)
2-Phenylamino pyrimidines	Imatinib	Tyrosine kinase inhibitors	OCT1 (41)	MDR1 (78) BCRP (138)

Regarding phase IIIa, there are several ATP-dependent mechanisms that account for the biliary secretion of anticancer drugs, whereas ATP-dependent and -independent systems account for phase IIIb, i.e. the transfer of anticancer drugs from cells towards the blood. These carriers are also involved in the transport of endogenous substances, such as bile acids, biliary pigments, nucleotides, nucleosides, steroid hormones and their metabolites, etc.

3.1. Transporters involved in the liver uptake of antineoplastic drugs

The basolateral transport proteins belonging to the gene superfamily of solute carriers, SLC, play a primordial role in the uptake of anticancer drugs by liver cells. Table 1 summarizes the transport systems that have been reported to be involved in the uptake of these compounds, classified according to their chemical structures and mechanisms of action.

3.1.1. OATPs (SLCO family)

An important role in the liver uptake of drugs is played by members of the organic anion transporting polypeptide (OATP) family, whose gene symbol was initially designated *SLC21A*, but was latter renamed as *SLCO* (1). The isoforms expressed in human hepatocytes are OATP-A/1A2, OATP-B/2B1, OATP-C/1B1 and OATP8/1B3 (2). The natural substrates of these transporters include several organic anions, such as bile acids, conjugated bilirubin (3), unconjugated bilirubin (4), as well as some neutral steroids and bulky type-II cations, such as quinidine. Although all isoforms share some substrate specificity, there are also peculiarities for each transporter in regard to this characteristic. Thus, OATP-C/1B1 is quantitatively the most important transporter involved in sodium-independent bile acid uptake by the liver. In contrast, OATP-B/2B1 is not able to transport bile acids (5). Although OATP-A/1A2, when expressed in *Xenopus laevis* oocytes is able to transport bile acids, owing to the very low expression of this protein in normal liver cells (2,6), its role in this function is probably minor as compared to those played by OATP-C/1B1 and the sodium-taurocholate cotransporting polypeptide NTCP (gene symbol *SLC10A1*).

Regarding anticancer drugs (Table 1), OATP-A/1A2 (7) and OATP8/1B3 (8) are able to transport the antimetabolite methotrexate, whereas 7-ethyl-10-hydroxycamptothecin (SN-38), an active metabolite of irinotecan, is a substrate for OATP-C/1B1. Thus, genetic polymorphisms in this transporter might contribute to the

well-known interindividual variability regarding the bioavailability of this topoisomerase inhibitor (9). OATP8/1B3, but not OATP-C/1B1, is able to transport paclitaxel with high affinity. However, it has not been possible to establish an association between the most frequent polymorphisms in the *SLCO1B3* gene, and the variations in the pharmacokinetics of this taxoid (10,11). Finally, it has been reported that Oatp2/1a4 is involved the transport of the antimetabolite hydroxyurea across the guinea-pig blood-brain barrier (12).

3.1.2. NTCP and ASBT (SLC10A family)

Members of the *SLC10A* gene family, such as the liver-specific NTCP, are able to carry out bile acid transport very efficiently (13,14). In particular, NTCP takes up bile acids across the sinusoidal membrane of hepatocytes with a stoichiometry of two Na^+ ions per molecule of bile acid, thanks to the sodium gradient maintained by Na^+,K^+-ATPase, located in the same membrane. NTCP is the main transporter accounting for the liver uptake of conjugated bile acids (e.g., taurocholate, tauroursodeoxycholate and taurochenodeoxycolate), but it is also able to transport, although with less efficiency, non conjugated bile acids (e.g., cholate), as well as other non-bile acid compounds, such as sulfated steroids (e.g., dehydroepiandrosterone sulfate and estrone sulfate), bromosulfophthalein and thyroid hormones (15,16).

Another member of this family of transporters, the apical sodium-dependent bile acid transporter (ASBT, gene symbol *SLC10A2*), is expressed in the apical membrane of cholangiocytes. This transporter is not liver-specific; the expression of ASBT has been also detected in the apical membrane of epithelial cells of the ileum of the hamster (17), rat (18), and humans (19), and of the proximal tubule in the kidney of rats (20) and humans (21).

Despite the fact that to date no anticancer drug has been reported to be a substrate of SLC10A transporters, these carriers are relevant for the issues addressed in the present review. This is because owing to their high efficiency in bile acid transport they are good candidates for use in drug targeting toward the liver (using NTCP) or intestine (using ASBT), as will be commented below. NTCP is able to transport chlorambucil if this is conjugated with taurocholate (22). Similarly, NTCP has been reported to transport several cisplatin-bile acid derivatives (23).

3.1.3. OATs (SLC22A family)

Anticancer drugs with very different mechanisms of action (Table 1) are substrates for the organic anion transporters (OATs) of the *SLC22A* family of genes (for a review, see 24). The first member of this family to be cloned was OAT1 (*SLC22A6*), which is expressed mainly in the kidney; specifically, in the basal membrane of proximal tubule epithelial cells. The isoforms OAT2 (*SLC22A7*), OAT4 (*SLC22A11*) and OAT5 (*SLC22A19*) are present in human liver (25). Indeed, OAT2 is predominantly expressed in the basal membrane of hepatocytes (26). It has been suggested that under physiological circumstances these transporters might play a role as export pathways, permitting the sinusoidal extrusion of compounds exported by the liver (27).

Several members of this family are able to transport methotrexate, such as the hepatic isoform OAT2 (25), but also OAT1, OAT3 and OAT4 (28). Other anticancer drugs that are substrates of OAT2 include 5-fluorouracil and paclitaxel (29). There is also evidence that OATs may be involved in determining the bioavailability of raloxifene, a drug used as a chemopreventive agent for breast cancer owing to its activity as a selective modulator of estrogen receptors (30).

OATs are also involved in transport of antineoplastic drugs in other tissues. For example, the rat isoform Oat3 has been reported to be involved in the transport across the blood-brain barrier of 6-mercaptopurine as well as other thiopurines (31). The cytotoxicity of the nucleotide analogs adefovir and cidofovir is enhanced in cells transfected with the renal isoform OAT1, suggesting that this carrier plays a role in the nephrotoxicity associated with treatments based on these antiviral agents (32).

3.1.4. OCTs and OCTNs (SLC22A family)

Organic cation transporters (OCTs) also belong to the SLC22A family. They carry out the Na^+-independent electrogenic transport of small cations (type I), such as tetraethylammonium (for a review, see 33,34). Three isoforms have been identified in humans: OCT1, OCT2 and OCT3 (*SLC22A1, SLC22A2, SLC22A3*, respectively). OCT1 is expressed in the basolateral membrane of hepatocytes (34,35). The family of *SLC22A* genes also includes the carnitine and cation transporters OCTN1 (*SLC22A4*) and OCT6 (*SLC22A16*) and the Na^+-carnitine cotransporter OCTN2 (*SLC22A5*), which can also behave as a Na^+-independent transporter of organic cations. OCTN1 and OCTN2 are expressed in human liver (33).

The accumulation, and hence toxicity, of oxaliplatin, but not that of cisplatin or carboplatin, has been reported to be markedly increased in cells transfected with OCT1, suggesting that oxaliplatin could be a good substrate for this transporter (36). OCT2, expressed in the nephron proximal tubule, is able to transport cisplatin, and has been suggested to be a major determinant in the nephrotoxicity induced by this cytostatic drug (37,38). Bleomycin, an antibiotic with anticancer activity, is transported in yeasts by a polyamine transport system (39), whose human ortholog is probably OCT1 (40). Imatinib, a phenylaminopyrimidine derivative commonly used to treat chronic myeloid leukemia, is also a substrate for OCT1, and it has been reported that the efficiency of OCT1-mediated imatinib uptake is a key determinant of the cellular response to this drug (41). There is also evidence that mitoxantrone is also transported by OCT1 (33).

OCT6 is involved in doxorubicin uptake, and indeed leukemia cells that over-express this transporter are

markedly more sensitive to the cytostatic activity of the drug (42). Although the expression of OCT6 is not detectable in human adult liver, this transporter is found in fetal liver as well as in several cell lines derived from human liver cancer (42).

3.1.5. Nucleoside transporters CNTs and ENTs (SLC28 and SLC29 families)

Nitrogenated base derivatives constitute an important group of anticancer drugs. Thus, purine-base analogs, such as 6-mercaptopurine and 6-thioguanine, and pyrimidine-base analogs, such as 5-fluorouracil and gemcitabine, are commonly used in the treatment of several types of cancer, including lymphocytic leukemia and acute myelocytic leukemia (43). Moreover, gemcitabine is efficient in the treatment of several cancers derived from epithelial cells located in the lung, pancreas, breast, bladder, ovaries and head and neck (44). As commented above, some of these agents are substrates of OATs (29,31). However, owing to their structural characteristics nucleoside transporters also play an important role in the uptake of these drugs by the liver (Table 1). Concentrative nucleoside transporters (CNTs), which belong to the *SLC28* gene family, are able to carry out the high-affinity sodium-dependent cotransport of nucleosides, whereas equilibrative nucleoside transporters (ENTs, gene family *SLC29*) are involved in the low-affinity uptake of a broad variety of nucleosides and their derivatives. Hepatocytes express CNT1 (*SLC28A1*) and CNT2 (*SLC28A2*), which have a certain preference for pyrimidine and purine nucleosides, respectively (45). These cells also express ENT1 (*SLC29A1*) and ENT2 (*SLC29A2*), which transport both purine and pyrimidine nucleosides. Thus, both 6-mercaptopurine and thioguanine are substrates of ENT2 (46,47) and CNT3 (46). Accordingly, a low expression of these carriers in tumor cells implies a reduced uptake and hence a certain resistance to these drugs (46). ENT2 does not transport 5-fluorouracil (47) but it does transport another pyrimidine analog, gemcitabine, which is a substrate of both ENT1 and ENT2, although that drug is transported with much higher affinity by CNT1 (48-50). CNT1 is probably also the transporter responsible for the uptake of 5´-deoxy-5-fluorouridine, the active metabolite of the oral anticancer drug capecitabine, a direct precursor of 5-fluorouracil (51).

3.1.6. Other transport systems involved in the uptake of antineoplastic drugs

In addition to those reported above, other members of the SLC superfamily play a role in the uptake of anticancer drugs. Among them, some examples will be described below. The copper transporter CTR1 (gene symbol *SLC31A1*) is involved in the uptake of platinum-related drugs, such as cisplatin, carboplatin and oxaliplatin (52). Reducing or abolishing the expression of this transporter in yeasts and in murine tumor cell lines results in an impaired intracellular accumulation of cisplatin and hence an enhanced resistance to this drug (53). Induction of resistance to cisplatin by continuous exposure in human colon carcinoma cells is accompanied by a down-regulation of CTR1 (54).

Melphalan, an alkylating phenylalanine derivative, is taken up via the L-type aminoacid transporter-1 (LAT-1, gene symbol *SLC7A5*) (55-57).

Finally is noteworthy that several antineoplastic compounds with lipophilic characteristics are able to cross the plasma membrane by simple diffusion without the intervention of any carrier protein. This seems to be the case of anthracyclines, such as doxorubicin and daunorubicin, or mitoxantrone. These are amphipatic molecules with a positive charge, which means that they may be recognized as substrates by OCTs (33,42) but also, because of their lipophilicity, they could be emplaced on the surface of membranes and cross them through a "flip-flop" process (58,59).

3.2. TRANSPORTERS INVOLVED IN THE EXPORT OF ANTICANCER DRUGS BY LIVER CELLS

Although they are not the only route determining the export of xenobiotics from liver cells towards the bile or the blood, several members of the superfamily of ATP-binding cassette (ABC) proteins account for the majority of these processes. Below we shall review those related to the role of members of several ABC families in the export of anticancer drugs, one of the most important mechanisms of resistance to chemotherapy. Table 1 summarizes the list of transport systems involved in the efflux of these compounds.

3.2.1. The ABCA family

So far, twelve members of this family have been identified in humans. However, only six of them are clearly expressed in the liver. These are ABCA1, 5, 6, 8, 9 and 10 (60,61). Their main physiological role is the transport of lipids across the plasma membrane and across the membrane of intracellular organelles. However, a role of these proteins in resistance to chemotherapy has been suggested based on the following data: i) some of them are able to transport cytostatic drugs, as is the case of ABCA8, which transports doxorubicin (62); ii) moreover, in chemotherapy-resistant cell lines an up-regulation of ABCA2 (63), ABCA3 (64) and ABCA6 (65) occurs. These findings suggest that ABCA transporters could play a role in enhancing the transfer of cytostatic drugs out from the cells or towards intracellular organelles, hence favoring their biotransformation or storage (61).

3.2.2. The ABCB family

This family of ABC proteins plays a key role among the mechanisms responsible for the export of potentially toxic endogenous and xenobiotic compounds. The multidrug resistance protein-1 (MDR1), or P-glycoprotein (gene symbol *ABCB1*), was the first to be identified and is the best studied (66). MDR1 is expressed in hepatocytes, cholangiocytes, lung, placenta, kidney and intestine, and also in many tumors of epithelial origin (67). In the latter case, its over-expression results in resistance to a large variety of compounds with very different structures and mechanisms of action (68). Thus, MDR1 is able to transport relatively hydrophobic organic cations (69),

cardiotonic glucosides, antihistaminics, analgesics, narcotics and immunosuppressants (for a review, see 67,70). Among the MDR1 substrates with antitumor activity (Table 1) are methotrexate (71), purine-base analogs (72), paclitaxel (73), vinca alkaloids (68), tamoxifen (74), amsacrine (75), bisantrene (76), anthracyclines (66), mitoxantrone (75), camptothecins (77), podophyllotoxins (68) and imatinib (78). Several polymorphisms in the *ABCB1* gene have been identified, some of which impair MDR1 function and modify the bioavailability of many drugs (79). Moreover, MDR1-dependent transport activity parallels the biotransforming activity of phase I and phase II enzymes (80). As an example, the CYP3A4 isoform of the cytochrome P450 system, which is one of the most abundant in the liver, together with MDR1 are key elements determining overall drug bioavailability (81). Thus, the coordinated action of both systems can reduce the bioavailability of certain drugs to less than 50% (82).

Although the main function of MDR3 (gene symbol *ABCB4*) in human hepatocytes, and its ortholog Mdr2 in rodents, is the translocation of phosphatidylcholine from the inner layer to the outer layer of the canalicular membrane (83), which is needed to neutralize the detergent effect of bile acids, this transporter is also involved in the transport of xenobiotics, including paclitaxel and vinblastine, although with less efficiency than MDR1 (84). This is probably why these compounds can impair MDR3-mediated phospholipid secretion, which is particularly evident in the presence of mutations that limit the functionality of this transporter (84).

The bile salt export pump (BSEP; gene symbol *ABCB11*) is the main mechanism responsible for bile acid secretion into bile (85). Like most ABC proteins, this pump uses the energy of ATP hydrolysis to transport monoanionic bile acids across the canalicular membrane into the bile with high affinity and efficiency (86,87). In addition to this physiological role, it has been shown that LLC-PK1 and MDCKII cells transfected with mouse Bsep are able to export some typical MDR1 substrates, such as vinblastine, but not daunorubicin or paclitaxel (88).

3.2.3. The ABCC family

Among the multidrug resistance-associated ABC proteins (MRPs) belonging to the ABCC family, the most abundantly expressed in the liver is MRP2 (gene symbol *ABCC2*). This transporter is expressed in the apical membrane of polarized cells, such as hepatocytes, but also in the renal tubule epithelium and intestinal mucosa. In the liver, this transporter plays an important role in the biliary secretion of endogenous and xenobiotic organic anions (89). Although it has broad substrate specificity, MRP2 has a higher affinity for compounds conjugated with glutathione, glucuronic acid, or sulfate and lipophilic compounds, such as leukotrien C4, bilirubin and some steroids (for review, see 90). At least rat Mrp2 has been shown to be able to transport dianionic bile acid species, either sulfated (91) or conjugated with glucuronic acid (92). Nonetheless, among MRP2 substrates there are also non-conjugated compounds, such as bromosulfophthalein and methotrexate, as well as glutathione, both reduced and oxidized. MRP2 is also able to transport several anticancer drugs (Table 1), such as chlorambucil (93), cyclophosphamide (94), methotrexate (95), vinca alkaloids (96), cisplatin (97), tamoxifen (30), anthracyclines (97), camptothecins (98) and podophyllotoxins (97). In addition to normal liver tissue, MRP2 is also expressed in many solid tumors, such as hepatocellular carcinoma, colorectal cancer, and cancers of lung, kidney and ovaries (99). This, together with its ability to confer resistance to many different drugs, explains the marked relevance of this transporter in clinical practice.

In addition to the canalicular isoform MRP2, there are also transporters of the MRP family expressed at the basal membrane of hepatocytes. These include MRP1 (*ABCC1*), MRP3 (*ABCC3*) and MRP4 (*ABCC4*), whose expression levels under physiological circumstances are low but that may increase in pathological conditions such as the Dubin-Johnson syndrome due to the existence of mutations in *ABCC2* gene or to cholestasis (100). These transporters may play a role in the extrusion of toxic compounds from normal hepatocytes and of anticancer drugs from tumor cells (Table 1). MRP1 is able to transport nitrogen mustards (101), oxazaphosphorines (94), methotrexate (95), mitoxantrone (102), camptothecins (103), vinca alkaloids, anthracyclines and etoposide (104). Among substrates of MRP4 are oxazaphosphorines (94), acyclic nucleosides (105), purine-base analogs (106), methotrexate (107) and camptothecins (108). Regarding antineoplastic drugs, MRP3 can transport methotrexate (109), whereas the also basolateral isoform MRP5 (gene symbol *ABCC5*) is able to transport purine-base analogs (110).

MRP6 (gene symbol *ABCC6*) is also expressed in hepatocytes (111) but its ability to behave as a drug-exporting system is probably low (112). MRP6 does not transport products resulting from phase I biotransformation (sulfated, glucuronidated or conjugated with glutathione), but does show a certain ability to transport cisplatin, doxorubicin and etoposide (113).

Other less studied members of this family are MRP7 and MRP8 (gene symbols *ABCC10* and *ABCC11*, respectively). The presence of MRP7 mRNA in many different tissues, including the liver, has been reported (114). When this transporter is transfected in cells *in vitro,* its ability to transport anticancer drugs such as paclitaxel and vincristine has been observed (114). Although at low levels, MRP8 mRNA has been also found in the liver, and this transporter has been shown to be able to transport methotrexate (115), fluorouracil (116) and acyclic nucleosides (117).

3.2.4. The ABCG family

Most members of the ABCG family are involved in sterol, mainly cholesterol, transport. This is the case of ABCG1, ABCG4, ABCG5 and ABCG8 (118). Among these, those with the highest expression levels in hepatocytes are ABCG5 and ABCG8, which form a heterodimeric protein located in the canalicular membrane

that is able to secrete cholesterol and other neutral sterols, such as sitosterols, into the bile (119,120).

The breast cancer resistance protein (BCRP; gene symbol *ABCG2*) shows broader substrate specificity than the rest of members of the ABCG family. Owing to the fact that among its substrates there are many anticancer drugs, the over-expression of this protein is considered to be a relevant problem in the treatment of solid tumors (118). The structure of BCRP consists of six transmembrane domains that include a single ATP-binding site (121). Thus, BCRP is considered a "half-transporter" that forms homodimers or oligomers (of up to twelve units) stabilized by disulfide bridges (122). In addition to the liver, prostate, small intestine and colon (123), ABCG2 is also highly expressed in placenta (124,125). Using immunohistochemistry techniques, the presence of BCRP in the apical membrane of hepatocytes, trophoblast cells, and epithelial cells of the intestinal mucosa has been detected (126,125).

Among the endogenous compounds transported by BCRP are porphyrins (127) and several sulfated steroids, including bile acids, estrone 3-sulfate and dehydroepiandrosterone sulfate (128,129). Moreover, BCRP can transport anticancer drugs such as oxazaphosphorines (94), methotrexate (130) and its glutamylated metabolites (131), flavopiridol (132), tamoxifen (133), bisantrene (121), doxorubicin and mitoxantrone (123,134), irinotecan and topotecan (135,136), etoposide (137) and imatinib (138).

Several mutations in the *ABCG2* gene have been reported. Most of them have been detected in tumor cells. These alter the expression, localization and transport activity of BCRP, which affect the pharmacokinetics of its substrates and the spectrum of anticancer drug resistance (139,140). Thus, cells expressing variant BCRP with the R482G and R482T mutations display enhanced resistance to anthracyclins and rhodamine 123 (141), but lack the ability to transport methotrexate (129). A frequent polymorphism, mainly in the Japanese population, is C421A, which is accompanied by a lower protein expression and a reduced ability to transport topotecan and irinotecan (142,143). In clinical practice, after the administration of diflomotecan, a topoisomerase I inhibitor, patients bearing this mutation present higher serum concentrations of this drug than people bearing wild-type BCRP (144). Another common polymorphism in this gene is G34A, which causes an alteration in protein targeting to the plasma membrane and reduces drug export ability of BCRP when expressed in cultured cells (143).

4. CHANGES IN THE FUNCTION OF BILIARY TRANSPORTERS INDUCED BY INTERACTIONS WITH ANTICANCER DRUGS

Owing to the broad substrate specificity of hepatobiliary transporters, there are many possible competitive effects between the substances that are transported by these carriers. This accounts for the interactions of the types: drug-drug, drug-food component and drug-endogenous substance. Some examples of these interaction involving anticancer drugs are reviewed below.

4.1. Drug-drug interactions

The fact that both the uptake and export systems for anticancer drugs share some degree of substrate specificity explains the possibility of drug-drug interactions at both levels. Some examples illustrating this situation are that OATP-C/1B1 is involved in the liver handling of the active metabolite of irinotecan SN-38 (9), which is exported by MDR1, MRP1, MRP2 and BCRP (98,145). Paclitaxel is also transported by OATP8/1B3 (10) and eliminated from the cells by MDR1 and MRP (146,114). The overall result of interactions with these transporters depends on the differential effect between uptake and export mechanisms.

As mentioned above, MDR1, MDR3, BSEP, MRP2 and BCRP are responsible for the biliary secretion of many different xenobiotics, including anticancer drugs (146-149). Most of them are eliminated from the body, mainly by the liver, after biotransformation. However, some anticancer drugs are partly excreted by the kidney, with or without previous biotransformation. The existence of drug-drug interactions could modify the proportion of the dose administered that is eliminated by the kidney, and the amount of drug that actually reaches the tumor cells, and which is then accumulated in them with ability to carry out its pharmacological activity. The existence of potential drug-drug interactions has been the basis of the development of novel strategies to overcome resistance to chemotherapy. This consists of the use of inhibitors of ABC proteins, named chemosensitizers because they are aimed at reducing drug efflux (excretion) and hence increasing effective intratumor levels. Most reported chemosensitizers are able to interfere with the function of MDR1 by inducing a competitive or non-competitive inhibition of this transporter, without being transported themselves (150). Among these modulating agents are verapamil, cyclosporine, valspodar, GF120918 and LY357739 (151,152). However, impaired ABC protein-mediated excretory function may also enhance the toxicity of anticancer drugs to healthy tissues, thus favoring the appearance of noxious side effects and limiting the usefulness of this strategy. Owing to the expression of MDR1 in the intestinal mucosa, the use of chemosensitizers for this transporter results in marked changes in the bioavailability of anticancer drugs when given orally. Thus, it has been reported that the administration of MDR1 inhibitors such as cyclosporine enhances the oral bioavailability of paclitaxel (153), etoposide (154) and doxorubicin (155) in humans. Verapamil increases the plasma concentrations of paclitaxel in women with breast cancer when both drugs are co-administered (156). Moreover, the oral administration of R101933 combined with i.v. administration of docetaxel has been assayed in humans with promising results, because the inhibition of MDR1 is not accompanied by major side effects or pharmacokinetic interactions in serum (157). In rodents, GF120918 increases the oral bioavailability of topotecan (158). MDR1 expression and function can be also modulated in an indirect manner, for instance, by

modifying the interaction with plasma membrane lipids (159) or the inhibition of protein kinase C (160).

It has been also proposed that the inhibition of bile secretion *via* Mrp and/or Mdr1 using cyclosporine A and probenecid increases the serum concentrations of irinotecan and their metabolites in rats (161-163). Moreover, probenecid-induced inhibition of rat Mrp2 reduces the biliary secretion of methotrexate (164).

Regarding BSEP, it has been suggested that BSEP-mediated resistance to paclitaxel in human ovary cancer cells can be reversed by cyclosporine A, PSC833 and verapamil (165).

The expression of hepatobiliary transporters can be modified by certain xenobiotics, which, in turn, can affect the bioavailability of anticancer drugs; either reducing their efficacy or enhancing their side effects. MDR1 expression in liver cells can be up-regulated by many different xenobiotics, such as carcinogens (e.g., 2-acethylaminofluorene, polycyclic hydrocarbon aromatics, 3-methylcholanthrene, benzo(α)pyreno, aflatoxin B1, methylmethane sulfonate and diethylnitrosamine) (166-170), phenothiazines and bromocriptine (166,171).

MRP2 expression can be induced by 2-acetylaminofluorene (172), the barbiturate phenobarbital (172,173), which also induces MRP3 (174,175), the chemopreventive agent oltipraz (176), the herbicide and peroxisome proliferator agent 2,4,5- trichlorophenoxyacetic acid (177), the anti-tuberculosis drug rifampicin, and the anti-estrogen tamoxifen (178). Cycloheximide is able to induce the expression of Mdr1b and Mrp2 in rat liver cells (179,180). Most of these compounds also induce up-regulation of detoxifying enzymes, which may result in more complex changes in the bioavailability of anticancer drugs in response to these xenobiotics (166). It is noteworthy that certain xenobiotics have the opposite effect, i.e., they inhibit the expression of export pumps. Thus, cytochalasin and colchicine reduce mRNA Mdr1b levels in primary rat hepatocytes (181), whereas nocodazol down-regulates human MRP2 in human hepatoma HepG2 cells (174).

4.2. Drug-nutrient interactions

Certain food components may also interact with hepatobiliary transporters, hence altering the bioavailability of anticancer drugs. Some of these interactions best studied are due to the inhibition of MDR1, MRPs and BCRP by flavonoids (182-185). Thus, quercetin inhibits doxorubicin transport in human breast cancer cells (186). In contrast, kaempferol, galangin and quercetin are able to stimulate doxorubicin export *via* MDR1 in human colon carcinoma cells (187). The reason for these apparent controversial results is not known. Genistein inhibits MDR1-mediated daunorubicin transport in human breast cancer cells (188). Both biochanin A and silymarin enhance the accumulation of daunomycin and doxorubicin in human breast cancer cells, and inhibit vinblastine efflux from Caco-2 cells (189). This is due to changes in MDR1 activity, without affecting its expression levels (190).

The interaction of flavonoids with MDR1 may also modify the distribution of drugs across normal epithelia, such as the blood brain barrier. Thus, at low concentrations, quercetin and kaempferol decrease the accumulation of vincristine in capillary endothelial cells from mouse brain, whereas at high levels these compounds have the opposite effect (191). Regarding *in vivo* studies, it has been demonstrated that flavone (192) and quercetin (193) enhance the bioavailability of paclitaxel in rats. An interesting coincidence is that most of the drugs that are transported by MDR1 are also substrates of CYP3A. It is also noteworthy that flavonoids can also inhibit CYP3A activity, which makes it difficult to distinguish whether drug-drug interactions affect one or both of these elements of the detoxification machinery when determining the overall pharmacological activity.

Interactions between flavonoids and MRP1 were first described by Versantvoort (194,195), who reported that genistein, biochanin A, apigenin and quercetin were able to inhibit MRP1-mediated daunorubicin transport in cancer cells. Some flavonoids present in the diet are able to modulate the transport of conjugates of glutathione with organic anions, drug resistance, and the ATPase activity of MRP1 (183). Thus, in human pancreatic adenocarcinoma cells, the flavonoids morin, chalcone, silymarin, phloretin, genistein, quercetin, biochanin A and kaempferol are able to inhibit the MRP1-mediated transport of daunomycin and vinblastine, which may be due to a direct interaction with MRP1 or to changes in the intracellular concentration of glutathione (196). Although MRP1 and MRP2 share a certain degree of substrate specificity, the structural requirements for flavonoids to be able to interact with these proteins are different, which account for the fact that fewer flavonoids are able to carry out a strong inhibition of MRP2 (197).

Regarding BCRP, the ability of many flavonoids to interact with this transporter has also been reported. Thus, silymarin, hesperetin, quercetin and daidzein, as well as stilbene resveratrol enhance the intracellular accumulation of mitoxantrone, whose extrusion is mediated by BCRP (198). This has been confirmed in different studies addressing the effect of 20 flavonoids potentially present in foods (apigenin, biochanin A, chrysin, daidzein, epigallocatechin, epigallocatechin-3-gallate, fisetin, genistein, hesperetin, kaempferol, luteolin, morin, myricetin, naringenin, naringin, phloretin, phloridzin, quercetin, silybin and silymarin) on BCRP-mediated mitoxantrone transport in human lung and breast cancer cells. Most of these compounds were found to be able to increase intracellular concentrations of mitoxantrone and overcome resistance to this drug. Chrysin and biochanin A seem to be the strongest BCRP inhibitors (185). It has been also shown that the flavonoids genistein, naringenin, hesperetin, acacetin, apigenin, chrysin, diosmetin, luteolin, galangin, kaempferide and kaempferol enhance the cytotoxicity of SN-38 and mitoxantrone in human leukemia cells expressing BCRP (199). To adequately evaluate the potential effect of food components, it is necessary to consider that they very often are present together and hence may have combined effects. Thus, when combined effects

of several flavonoids (apigenin, biochanin A, chrysin, genistein, kaempferol, hesperetin, naringenin and silymarin) on BCRP-mediated mitoxantrone transport were evaluated in human breast cancer cells, an additive effect was observed (184). This has lead to the suggestion that "flavonoid cocktails" may be useful to overcome drug resistance in cancer chemotherapy. Moreover, the combined effects with other non-flavonoid food components that may also inhibit BCRP, such as isothiocyanates, must also be considered (200). *In vivo* studies have shown that although chrysin and benzoflavone inhibit BCRP-mediated topotecan transport in human breast cancer cells, combined treatment of chrysin and benzoflavone fails to further enhance the oral bioavailability of this compound in rats and Mdr1a/1b knock-out mice (158). The reason for such results is probably the low sensitivity of rodent Bcrp to inhibition by flavonoids, as has been demonstrated in transfected MDCK kidney cells.

Grapefruit juice, which contains high levels of flavonoids, may impair intestinal MDR1 activity without affecting its expression. Thus, grapefruit juice can inhibit MDR1-mediated vinblastine efflux from Caco-2 cells (201). Moreover, grapefruit juice stimulates the efflux of vinblastine and other MDR1 substrates across the basal membrane of MDCK cells. In humans, grapefruit juice has been reported to reduce the bioavailability of etoposide (202) and other drugs (203). It should be considered that flavonoid-rich food, such as grapefruit, may also affect the overall uptake of drugs by interaction with OATP-C/1B1 (204).

4.3. Interactions between drugs and endogenous compounds

The interaction between anticancer drugs and hepatobiliary transporters may also affect the liver uptake and biliary secretion of endogenous compounds. In this sense, jaundice has been reported after combined administration to patients of cyclosporine with daunorubicin (205), doxorubicin (155) or etoposide (154). Inversely, the elevated levels of certain endogenous substances may affect the handling of anticancer drugs by hepatobiliary transporters. Thus, bile acids reduce the overall hepatobiliary elimination of cisplatin in rats, even though they induce a more marked secretion of cisplatin from hepatocytes into bile (206).

Several hormones may affect the expression of the pumps involved in drug elimination into bile, such as MDR1, BSEP and MRP2 (207). Hydroxylated steroids, including cortisol, dexamethasone, aldosterone and corticosterone, can be exported by MDR1, whereas progesterone cannot be transported by this pump (208), but behaves as a modulator of the activity of this transporter (209). MDR1-dependent resistance of several cell lines to vinblastine and doxorubicin can be overcome by anti-estrogens, such as tamoxifen and toremifen (210), and anti-progestins, such as RU 486 (211). Other hormones able to modulate these transporters and that might affect the bioavailability of anticancer drugs are insulin (212), insulin-like growth factor-I (213) and some pituitary hormones (214) able to induce Mdr1 expression in rodent liver cells. In rat hepatocytes, glucocorticoids induce an up-regulation of Mrp2 (215) and Bsep (216), whereas prolactin enhances Bsep expression in the livers of ovariectomized rats (217,218).

Conjugation with glutathione followed by extrusion of the conjugates *via* MRPs is an important detoxification pathway for many anticancer drugs. Indeed, the levels of glutathione, conjugating enzymes and MRP expression are increased in many types of drug-resistant cancer cells. This suggests that glutathione levels might modify the cellular response to treatment with anticancer drugs. In general, a decrease in the cellular content of glutathione would enhance the accumulation of active drug, whereas high intracellular glutathione levels would favor the efflux process (219). Some anticancer drugs, such as vincristine can be co-transported with glutathione by MRP1 (220).

5. EFFECT OF ANTICANCER DRUGS ON THE EXPRESSION OF HEPATOBILIARY TRANSPORTERS

Another interesting aspect of the relationship between anticancer drugs and hepatobiliary transporters is that the expression of these proteins can be modified by exposure to these drugs. Thus, MDR1 has been found to be up-regulated in the liver of patients treated with antineoplastic agents, possibly reflecting an adaptive response aimed at increasing the biliary elimination of the drug and its metabolites (221,222).

The expression of ABC proteins can be increased in response to exposure to very structurally different compounds. Even compounds that are not substrates of MDR1 have been found to increase the levels of MDR1 mRNA in tumor cell lines, resulting in a multidrug resistance phenotype (223). For instance, in primary cultures of rat hepatocytes acute treatment with anthracyclins, such as doxorubicin or daunorubicin, or with mitoxantrone, stimulate the expression of Mdr1b (224,225). Mitoxantrone has also been found to induce an up-regulation of Mdr1 *in vivo* both in the liver and intestine of rats but not those of mice (224).

Cultured rat hepatocytes up-regulate Mrp2 when they are exposed to cisplatin (180). This agent is also able to induce the expression of MRP2, MRP3 and MRP5 in human cell lines of hepatic origin (226). Tamoxifen is also able to induce MRP2 expression in the liver of non-human primates (178). The mechanism accounting for these changes is not well known, but it has been suggested that reactive oxygen species would trigger, either directly or through an alteration of intracellular macromolecules such as DNA, the defensive response (227). In support of this concept is the fact that the daunorubicin-induced up-regulation of rat Mdr1b is dependent on p53 (228).

Over the past few years, the key role played by nuclear receptors in the control of the expression of hepatobiliary transporters has become evident. Some

members of this superfamily of transcription factors are dependent on the interaction with a ligand, which, in some cases, could be a xenobiotic compound, suggesting that they would behave as "xenosensors" (for a review, see 229). This is the case of the constitutive androstane receptor (CAR) and the steroid and xenobiotic X receptor/pregnane X receptor (SXR/PXR). Both form heterodimeric complexes with the retinoid X receptor (RXR) to activate the promoters of the enzymes and transporters involved in the detoxification of the ligand by the liver (for a review, see 230). Thus, CAR activators, such as phenobarbital, induce the expression of MRP2 (231) and MRP4 (232), and probably also MDR1 (233). Rifampicin and other PXR ligands stimulate the expression in the liver of MDR1 (234,235), MRP2 (231), MRP3 (236,237) and Oatp2/1a4 (238).

Among the ligands of these nuclear receptors are several drugs with anticancer activity, such as cisplatin and paclitaxel. In contrast to the structurally related carboplatin and docetaxel, respectively, the former are able to strongly activate PXR, and hence induce the expression of MDR1 (235,239). Other anticancer drugs with the ability to activate PXR are topotecan and etoposide (240).

The opposite effect has also been described. Thus, ecteinascidin-743 (ET-743), a strong cytostatic agent of marine origin that has been used in clinical practice to treat sarcoma and breast and ovary cancer, has been found to down-regulate MDR1 by antagonizing human PXR *in vitro* (235). However, these findings are not consistent with those obtained *in vivo* using rats treated with ET-743. In these animals, an up-regulation of hepatic Mdr1a and Mdr1b has been found (241).

Diallyl sulfide is a chemopreventive agent obtained from garlic that affords efficient protection against stomach and colon cancer. Moreover, diallyl sulfide induces the expression of Mrp2 in rat kidney, an effect that is enhanced when it is administered in combination with cisplatin, which may constitute an additional stimulus for a defensive response to be elicited (242). Response to diallyl sulfide has been reported to be mediated by the activation of CAR (243).

Finally, it should be mentioned that several cytostatic drugs are direct ligands of RXR. This is the case of bexaroten (Targretin), which is a potent selective ligand of RXR (244). Since RXR is the mandatory partner of other nuclear receptors, such as PXR, CAR and the bile acid sensor farnexoid X receptor (FXR), changes in RXR could have more profound and complex repercussions in the expression of hepatobiliary transporters. Indeed, in the liver of rats treated with bexaroten up-regulation of canalicular Bsep has been found (245), this carrier being known to be activated by the heterodimer FXR:RXR (246).

6. EXPRESSION OF HEPATOBILIARY TRANSPORTERS IN TUMORS OF THE ENTEROHEPATIC CIRCUIT

The expression of hepatobiliary transporters in tumors of the liver, gallbladder, biliary tree and intestine can be markedly different to that present in normal tissues. Owing to the phenotypic diversity of the tumors affecting these organs it is not possible to establish a common pattern of reduction or loss of transporters involved in the uptake and export of cholephilic organic anions.

Several tumor cell lines of hepatic origin maintain the expression of NTCP and some members of the OATP family, although the ability to transport, for instance bile acids, is usually reduced (247-250). Thus, using HepG2 cells, which are derived from human hepatoblastoma, different groups have demonstrated that in spite of the detectable presence of the mRNA of OATP-C/1B1, OATP8/1B3 and OATP3A1, although at lower levels than in healthy tissue (251), none of these isoforms could be detected by immunohistochemistry, whereas the expression of OATP-B/2B1, OAT2 and OAT3 were maintained or even increased (252).

When rat liver cells were obtained after undergoing chemical induction of hepatocarcinogenesis, these cells were able to take up bile acids. Sodium-independent mechanisms were better preserved than sodium-dependent processes, which suggest that during carcinogenesis the expression of sodium-independent uptake transporters of organic anions is more resistant to the loss of phenotypic characteristics typical of healthy adult hepatocytes (253).

In agreement with these findings, other authors have reported that the expression of NTCP in human hepatocellular carcinoma is lower than that in the surrounding healthy tissue. In contrast, that of OATP is similar in both healthy and tumor liver tissue (22). However, more recently, other groups have reported a markedly reduced expression of both NTCP and OATP-C/1B1 in the majority of hepatocellular carcinomas assayed (254). Similar results were found for OATP8/1B3 (251,252). None of these isoforms of OATPs were found expressed in cholangiocarcinomas or metastatic liver cancer (251). However, the abundance of the mRNA of some hepatobiliary transporters in colorectal adenomas and carcinomas has been found to be consistent with possible transport ability. Indeed, when total mRNA was injected into *Xenopus laevis* oocytes, this conferred them the capability to take up bile acids and cytostatic bile acids derivatives (255).

In non-cirrhotic livers with hepatocellular adenomas, the expression of OATP-C/1B1 and OATP8/1B3 is very low or absent, whereas in focal nodular hyperplasia these isoforms are up-regulated, although their expression is dispersed, as observed by immunohistochemistry (256). NTCP, OATP-C/1B1 and OATP8/1B3 expression was reduced in patients with primary biliary cirrhosis (257,258), in parallel with the degree of injury and jaundice.

It is important to highlight that in spite of the reduction in the expression or/and functionality of transport proteins in tumor cells, the overall load of substrates (e.g., cytostatic drugs) could be enhanced due to the lack of polarity, which could prolong the intracellular residence of

the compounds taken up. Thus, when platinated bile acid derivatives were administered to nude mice bearing an orthotopically implanted liver tumor of murine origin from Hepa 1-6 cells, the amount of drug found in the tumor was higher than that measured in the surrounding healthy tissue (259). This is important, because there is a relationship between the efficacy and intracellular concentrations of these drugs (260).

Regarding export mechanisms, it has been reported that the expression of both canalicular MDR1, MDR3 and BSEP and basolateral MRP3 is reduced in a highly variable pattern among the different types of hepatocellular carcinoma. Marked variability also exists among individuals within the same type of tumor (254). In contrast, in hepatocellular carcinoma the expression levels of MRP2 are generally maintained or even show a trend towards increased levels (254).

7. TARGETING OF CYTOSTATIC DRUGS USING HEPATOBILIARY TRANSPORTERS

The goal of the targeting of anticancer drugs is to increase the concentration of pharmacologically active agents in tumor cells and, if possible, to reduce the exposure of healthy tissues and hence minimize the side effects of the treatment. One of the different strategies devised is based on the specificity of interactions between macromolecules (e.g., receptors, transporters, enzymes, etc) and smaller biomolecules, which have been used as Trojan Horses to shuttle cytostatic agents. Much effort has been devoted to taking advantage of the efficient uptake of cholephilic organic anions, such as bile acids, by transporters expressed in both hepatic and intestinal cells for use as molecular targets for directing anticancer drugs towards tumors of the enterohepatic circuit (261). The usefulness of bile acids in obtaining targeted drugs is based on their versatile derivatization possibilities, rigid steroidal backbone, enantiomeric purity, availability, and the low cost of natural bile acids for use in chemical reactions (for a review, see 262-264). This pharmacological tool has been investigated for the targeting of very different types of drugs; not only anticancer agents (265-268). Bile acids are versatile building blocks to which many different substances can be attached at different positions of the steroidal skeleton or on the side chain *via* different chemical bonds, which can be further varied by linkers with different structures, lengths, stereochemistries, polarities, and/or functional groups. A key aspect in designing these drugs is to know which regions of the bile acid interact with the carrier and which ones might be used for chemical derivatization to bind the active agent. In principle, the possibilities for conjugating a drug to a bile acid include hydroxyl groups, in particular the one located at the 3α-position, and the carboxyl group on the side chain.

Members of the SLC10A family, such as NTCP in hepatocytes and ASBT in cells of the intestinal epithelium and cholangiocytes, which are highly efficient in transporting bile acids, have been reported to interact with the region of the bile acid that contains its side chain (269). Consequently, to target bile acid derivatives to tissues expressing these transporters, this part of the molecule must not be used to bind the active agent. Although the efficiency is lower, the expression of OATPs is in general better preserved in tumor cells. Several members of the human OATP family have been shown to be able to transport bile acid derivatives obtained by coupling an active agent to the bile acid side chain (23).

Both strategies have been used to obtain cytostatic bile acid derivatives carrying a coupling agent, such as chlorambucil (270), and other organic moieties (271) as well as inorganic agents, such as platinum- and gold-based drugs (for a review, see 262). The latter are particularly interesting because of the small size of the resulting molecule, which would increase the probability of maintaining both substrate properties as regards bile acid transporters and reactivity versus DNA, and hence the antiproliferative effect of these metals, in particular platinum(II) such as in cisplatin - cis-diamminedichloro platinum(II) - (272). Two of the best studied and most promising compounds of this family of drugs are cis-diamminechloro-cholylglycinate platinum(II) (Bamet-R2) (273) and the more active and less toxic antitumor agent cis-diammine-bisursodeoxycholate platinum(II) (Bamet-UD2) (274). Derivatives containing transition metal atoms other than platinum, such as gold (275), are less efficient cytostatic agents than those containing platinum(II) in the reactive moiety. Regarding the organic moiety of the molecule, different derivatives have been obtained by changing either the bile acid moiety or the linker between this and the DNA-reactive moiety (261). The list of these derivatives has been expanded by the synthesis of several carboplatin-bile acid derivatives (276).

Although cytostatic bile acid derivatives were first synthesized to enhance their water miscibility (277) or to target antitumor agents toward tumors located in tissues of the enterohepatic circuit (261) they have the additional advantage of being efficiently taken up by the liver and eliminated into bile. This reduces the amount of drug that, escaping from the tumor, might reach the general circulation during regional therapy (278,279).

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9. REFERENCES

1. B. Hagenbuch and P. J. Meier: Organic anion transporting polypeptides of the OATP/SLC21 family: phylogenetic classification as OATP/SLCO super-family, new nomenclature and molecular/functional properties. *Pflugers Arch* 447, 653-665 (2004)

2. B. Hagenbuch and P. J. Meier: The superfamily of organic anion transporting polypeptides. *Biochim Biophys Acta* 1609, 1-18 (2003)

3. Y. Cui, J. Konig, I. Leier, U. Buchholz and D. Keppler: Hepatic uptake of bilirrubin and its conjugates by the human organic anion-transporting polypeptide SLC21A6. *J Biol Chem* 276, 9626-9630 (2001)

4. O. Briz, M. A. Serrano, R. I. Macias, J. Gonzalez-Gallego and J. J. G. Marin: Role of organic anion-transporting polypeptides, OATP-A, OATP-C and OATP-8 in the human placenta-maternal liver tandem excretory pathway for foetal bilirubin. *Biochem J* 371, 897-905 (2003)

5. G. A. Kullak-Ublick, M. G. Ismair, B. Stieger, L. Landmann, R. Huber, F. Pizzagalli, K. Fattinger, P. J. Meier and B. Hagenbuch: Organic anion-transporting polypeptide B (OATP-B) and its functional comparison with three other OATPs of human liver. *Gastroenterology* 120, 525-533 (2001)

6. E. Jigorel, M. Le Vee, C. Boursier-Neyret, M. Bertrand and O. Fardel: Functional expression of sinusoidal drug transporters in primary human and rat hepatocytes. *Drug Metab Dispos* 33, 1418-1422 (2005)

7. I. Badagnani, R. A. Castro, T. R. Taylor, C. M. Brett, C. C. Huang, D. Stryke, M. Kawamoto, S. J. Johns, T. E. Ferrin, E. J. Carlson, E. G. Burchard and K. M. Giacomini: Interaction of methotrexate with organic-anion transporting polypeptide 1A2 and its genetic variants. *J Pharmacol Exp Ther* 318, 521-529 (2006)

8. T. Abe, M. Unno, T. Onogawa, T. Tokui, T. N. Kondo, R. Nakagomi, H. Adachi, K. Fujiwara, M. Okabe, T. Suzuki, K. Nunoki, E. Sato, M. Kakyo, T. Nishio, J. Sugita, N. Asano, M. Tanemoto, M. Seki, F. Date, K. Ono, Y. Kondo, K. Shiiba, M. Suzuki, H. Ohtani, K. Shimosegawa, K. Iinuma, H. Nagura, S. Ito and S. Matsuno: LST-2, a human liver-specific organic anion transporter, determines methotrexate sensitivity in gastrointestinal cancers. *Gastroenterology* 120, 1689-1699 (2001)

9. T. Nozawa, H. Minami, S. Sugiura, A. Tsuji and I. Tamai: Role of organic anion transporter OATP1B1 (OATP-C) in hepatic uptake of irinotecan and its active metabolite, 7-ethyl-10-hydroxycamptothecin: *in vitro* evidence and effect of single nucleotide polymorphisms. *Drug Metab Dispos* 33, 434-439 (2005)

10. N. F. Smith, M. R. Acharya, N. Desai, W. D. Figg, A. Sparreboom, B. Hagenbuch, B. Ugele, P. J. Meier and T. Stallmach: Identification of OATP1B3 as a high-affinity hepatocellular transporter of paclitaxel. *Cancer Biol Ther* 4, 815-818 (2005)

11. N. F. Smith, S. Marsh, T. J. Scott-Horton, A. Hamada, S. Mielke, K. Mross, W. D. Figg, J. Verweij, H. L. McLeod and A. Sparreboom: Variants in the SLCO1B3 gene: interethnic distribution and association with paclitaxel pharmacokinetics. *Clin Pharmacol Ther* 81, 76-82 (2007)

12. M. Dogruel, J. E. Gibbs and S. A. Thomas: Hydroxyurea transport across the blood-brain and blood-cerebrospinal fluid barriers of the guinea-pig. *J Neurochem* 87, 76-84 (2003)

13. B. Hagenbuch, B. Stieger, M. Foguet, H. Lubbert and P. J. Meier: Functional expression cloning and characterization of the hepatocyte Na+/bile acid co-transport system. *Proc Natl Acad Sci U S A* 88, 10629-10633 (1991)

14. B. Hagenbuch and P. J. Meier: Molecular cloning, chromosomal localization and functional characterization of a human liver Na+/bile acid cotransporter. *J Clin Invest* 93, 1326-1331 (1994)

15. P. J. Meier, U. Eckhardt, A. Schroeder, B. Hagenbuch and B. Stieger: Substrate specificity of sinusoidal bile acid and organic anion uptake systems in rat and human liver. *Hepatology* 26, 1667-1677 (1997)

16. E. C. Friesema, R. Docter, E. P. Moerings, B. Stieger, B. Hagenbuch, P. J. Meier, E. P. Krenning, G. Hennemann and T. J. Visser: Identification of thyroid hormone transporters. *Biochem Biophys Res Commun* 254, 497-501 (1999)

17. M. H. Wong, P. Oelkers, A. L. Craddock and P. A. Dawson: Expression cloning and characterization of the hamster ileal sodium-dependent bile acid transporter. *J Biol Chem* 269, 1340-1347 (1994)

18. B. L. Shneider, P. A. Dawson, D. M. Christie, W. Hardikar, M. H. Wong and F. J. Suchy: Cloning and molecular characterization of the ontogeny of a rat ileal sodium-dependent bile acid transporter. *J Clin Invest* 95, 745-754 (1995)

19. M. H. Wong, P. Oelkers and P. A. Dawson: Identification of a mutation in the ileal sodium-dependent bile acid transporter gene that abolishes transport activity. *J Biol Chem* 270, 27228-27234 (1995)

20. D. M. Christie, P. A. Dawson, S. Thevananther and B. L. Shneider: Comparative analysis of the ontogeny of a sodium-dependent bile acid transporter in rat kidney and ileum. *Am J Physiol* 271, G377-G385 (1996)

21. A. L. Craddock, M. V. Love, R. W. Daniel, L. C. Kirby, H. C. Walters, M. H. Wong and P. A. Dawson: Expression and transport properties of the human ileal and renal sodium-dependent bile acid transporter. *Am J Physiol* 274, G157-G169 (1998)

22. G. A. Kullak-Ublick, J. Glasa, C. Boker, M. Oswald, U. Grutzner, B. Hagenbuch, B. Stieger, P. J. Meier, U. Beuers, W. Kramer, G. Wess and G. Paumgartner: Chlorambucil-taurocholate is transported by bile acid carriers expressed in human hepatocellular carcinomas. *Gastroenterology* 113, 1295-1305 (1997)

23. O. Briz, M. A. Serrano, N. Rebollo, B. Hagenbuch, P. J. Meier, H. Koepsell and J. J. G. Marin: Carriers involved in targeting the cytostatic bile acid-cisplatin derivatives cis-diammine-chloro-cholylglycinate-platinum(II) and cis-diammine-bisurso deoxycholate-platinum(II) toward liver cells. *Mol Pharmacol* 61, 853-860 (2002)

24. H. Miyazaki, T. Sekine and H. Endou: The multispecific organic anion transporter family: properties and pharmacological significance. *Trends Pharmacol Sci* 25, 654-662 (2004)

25. W. Sun, R. R. Wu, P. D. van Poelje and M. D. Erion: Isolation of a family of organic anion transporters from human liver and kidney. *Biochem Biophys Res Commun* 283, 417-422 (2001)

26. T. Sekine, S. H. Cha, M. Tsuda, N. Apiwattanakul, N. Nakajima, Y. Kanai and H. Endou: Identification of multispecific organic anion transporter 2 expressed predominantly in the liver. *FEBS Lett* 429, 179-182 (1998)

27. G. A. Kullak-Ublick, U. Beuers and G. Paumgartner: Hepatobiliary transport. *J Hepatol* 32, 3-18 (2000)

28. M. Takeda, S. Khamdang, S. Narikawa, H. Kimura, M. Hosoyamada, S. H. Cha, T. Sekine and H. Endou: Characterization of methotrexate transport and its drug interactions with human organic anion transporters. *J Pharmacol Exp Ther* 302, 666-671 (2002)

29. Y. Kobayashi, N. Ohshiro, R. Sakai, M. Ohbayashi, N. Kohyama and T. Yamamoto: Transport mechanism and substrate specificity of human organic anion transporter 2 (hOat2 [SLC22A7]). *J Pharm Pharmacol* 57, 573-578 (2005)

30. E. J. Jeong, H. Lin and M. Hu: Disposition mechanisms of raloxifene in the human intestinal Caco-2 model. *J Pharmacol Exp Ther* 310, 376-385 (2004)

31. S. Mori, S. Ohtsuki, H. Takanaga, T. Kikkawa, Y. S. Kang and T. Terasaki: Organic anion transporter 3 is involved in the brain-to-blood efflux transport of thiopurine nucleobase analogs. *J Neurochem* 90, 931-941 (2004)

32. E. S. Ho, D. C. Lin, D. B. Mendel and T. Cihlar: Cytotoxicity of antiviral nucleotides adefovir and cidofovir is induced by the expression of human renal organic anion transporter 1. *J Am Soc Nephrol* 11, 383-393 (2000)

33. H. Koepsell, K. Lips and C. Volk: Polyspecific organic cation transporters: Structure, function, physiological roles, and biopharmaceutical implications. *Pharm Res* 24, 1227-1251 (2007)

34. J. W. Jonker and A. H. Schinkel: Pharmacological and physiological functions of the polyspecific organic cation transporters: OCT1, 2, and 3 (SLC22A1-3). *J Pharmacol Exp Ther* 308, 2-9 (2004)

35. L. Zhang, M. J. Dresser, A. T. Gray, S. C. Yost, S. Terashita and K. M. Giacomini: Cloning and functional expression of a human liver organic cation transporter. *Mol Pharmacol* 51, 913-921 (1997)

36. S. Zhang, K. S. Lovejoy, J. E. Shima, L. L. Lagpacan, Y. Shu, A. Lapuk, Y. Chen, T. Komori, J. W. Gray, X. Chen, S. J. Lippard and K. M. Giacomini: Organic cation transporters are determinants of oxaliplatin cytotoxicity. *Cancer Res* 66, 8847-8857 (2006)

37. G. Ciarimboli, T. Ludwig, D. Lang, H. Pavenstadt, H. Koepsell, H. J. Piechota, J. Haier, U. Jaehde, J. Zisowsky and E. Schlatter: Cisplatin nephrotoxicity is critically mediated via the human organic cation transporter 2. *Am J Pathol* 167, 1477-1484 (2005)

38. A. Yonezawa, S. Masuda, K. Nishihara, I. Yano, T. Katsura and K. Inui: Association between tubular toxicity of cisplatin and expression of organic cation transporter rOCT2 (Slc22a2) in the rat. *Biochem Pharmacol* 70, 1823-1831 (2005)

39. M. Aouida, A. Leduc, H. Wang and D. Ramotar: Characterization of a transport and detoxification pathway for the antitumour drug bleomycin in *Saccharomyces cerevisiae*. *Biochem J* 384, 47-58 (2004)

40. H. Koepsell: Organic cation transporters in intestine, kidney, liver, and brain. *Annu Rev Physiol* 60, 243-266 (1998)

41. D. L. White, V. A. Saunders, P. Dang, J. Engler, A. C. Zannettino, A. C. Cambareri, S. R. Quinn, P. W. Manley and T. P. Hughes: OCT-1-mediated influx is a key determinant of the intracellular uptake of imatinib but not nilotinib (AMN107): reduced OCT-1 activity is the cause of low *in vitro* sensitivity to imatinib. *Blood* 108, 697-704 (2006)

42. M. Okabe, M. Unno, H. Harigae, M. Kaku, Y. Okitsu, T. Sasaki, T. Mizoi, K. Shiiba, H. Takanaga, T. Terasaki, S. Matsuno, I. Sasaki, S. Ito and T. Abe: Characterization of the organic cation transporter SLC22A16: a doxorubicin importer. *Biochem Biophys Res Commun* 333, 754-762 (2005)

43. G. H. Elgemeie: Thioguanine, mercaptopurine: their analogs and nucleosides as antimetabolites. *Curr Pharm Des* 9, 2627-2642 (2003)

44. C. J. Allegra and J. L. Grem: Antimetabolites. In: V. T. De-Vita Jr, ed. Cancer: Principles and Practice of Oncology. Philadelphia: *Lippincott-Raven* 490-498 (1997)

45. A. Felipe, R. Valdes, B. Santo, J. Lloberas, J. Casado and M. Pastor-Anglada: Na+-dependent nucleoside transport in liver: two different isoforms from the same gene family are expressed in liver cells. *Biochem J* 330, 997-1001 (1998)

46. A. K. Fotoohi, M. Lindqvist, C. Peterson and F. Albertioni: Involvement of the concentrative nucleoside transporter 3 and equilibrative nucleoside transporter 2 in the resistance of T-lymphoblastic cell lines to thiopurines. *Biochem Biophys Res Commun* 343, 208-215 (2006)

47. K. Nagai, K. Nagasawa, Y. Kihara, H. Okuda and S. Fujimoto: Anticancer nucleobase analogues 6-mercaptopurine and 6-thioguanine are novel substrates for equilibrative nucleoside transporter 2. *Int J Pharm* 333, 56-61 (2007)

48. J. R. Mackey, S. Y. Yao, K. M. Smith, E. Karpinski, S. A. Baldwin, C. E. Cass and J. D. Young: Gemcitabine transport in *Xenopus* oocytes expressing recombinant plasma membrane mammalian nucleoside transporters. *J Natl Cancer Inst* 91, 1876-1881 (1999)

49. J. Garcia-Manteiga, M. Molina-Arcas, F. J. Casado, A. Mazo and M. Pastor-Anglada: Nucleoside transporter profiles in human pancreatic cancer cells: role of hCNT1 in 2',2'-difluorodeoxycytidine-induced cytotoxicity. *Clin Cancer Res* 9, 5000-5008 (2003)

50. J. H. Gray, R. P. Owen and K. M. Giacomini: The concentrative nucleoside transporter family, SLC28. *Pflugers Arch* 447, 728-734 (2004)

51. J. F. Mata, J. M. Garcia-Manteiga, M. P. Lostao, S. Fernandez-Veledo, E. Guillen-Gomez, I. M. Larrayoz, J. Lloberas, F. J. Casado and M. Pastor-Anglada: Role of the human concentrative nucleoside transporter (hCNT1) in the cytotoxic action of 5´-deoxy-5-fluorouridine, an active intermediate metabolite of capecitabine, a novel oral anticancer drug. *Mol Pharmacol* 59, 1542-1548 (2001)

52. R. Safaei and S. B. Howell: Copper transporters regulate the cellular pharmacology and sensitivity to Pt drugs. *Crit Rev Oncol Hematol* 53, 13-23 (2005)

53. S. Ishida, J. Lee, D. J. Thiele and I. Herskowitz: Uptake of the anticancer drug cisplatin mediated by the copper transporter Ctr1 in yeast and mammals. *Proc Natl Acad Sci U S A* 99, 14298-14302 (2002)

54. M. J. Monte, M. R. Ballestero, O. Briz, M. J. Perez and J. J. G. Marin: Pro-apoptotic effect on normal and tumor intestinal cells of cytostatic drugs with enterohepatic organotropism. *J Pharmacol Exp Therap* 315, 24-35 (2005)

55. J. Lin, D. A. Raoof, D. G. Thomas, J. K. Greenson, T. J. Giordano, G. S. Robinson, M. J. Bourner, C. T. Bauer, M. B. Orringer and D. G. Beer: L-type amino acid transporter-1 overexpression and melphalan sensitivity in Barrett's adenocarcinoma. *Neoplasia* 6, 74-84 (2004)

56. Y. Takada, N. H. Greig, D. T. Vistica, S. I. Rapoport and Q. R. Smith: Affinity of antineoplastic amino acid drugs for the large neutral amino acid transporter of the blood-brain barrier. *Cancer Chemother Pharmacol* 29, 89-94 (1991)

57. N. H. Greig, S. Momma, D. J. Sweeney, Q. R. Smith and S. I. Rapoport: Facilitated transport of melphalan at the rat blood-brain barrier by the large neutral amino acid carrier system. *Cancer Res* 47, 1571-1576 (1987)

58. G. Decorti, I. Peloso, D. Favarin, F. B. Klugmann, L. Candussio, E. Crivellato, F. Mallardi and L. Baldini: Handling of doxorubicin by the LLC-PK1 kidney epithelial cell line. *J Pharmacol Exp Ther* 286, 525-530 (1998)

59. R. Regev, D. Yeheskely-Hayon, H. Katzir and G. D. Eytan: Transport of anthracyclines and mitoxantrone across membranes by a flip-flop mechanism. *Biochem Pharmacol* 70, 161-169 (2005)

60. A. Zarubica, D. Trompier and G. Chimini: ABCA1, from pathology to membrane function. *Pflugers Arch* 453, 569-579 (2007)

61. C. Albrecht and E. Viturro: The ABCA subfamily-gene and protein structures, functions and associated hereditary diseases. *Pflugers Arch* 453, 581-589 (2007)

62. S. Tsuruoka, K. Ishibashi, H. Yamamoto, M. Wakaumi, M. Suzuki, G. J. Schwartz, M. Imai and A. Fujimura: Functional analysis of ABCA8, a new drug transporter. *Biochem Biophys Res Commun* 298, 41-45 (2002)

63. N. M. Laing, M. G. Belinsky, G. D. Kruh, D. W. Bell, J. T. Boyd, L. Barone, J. R. Testa and K. D. Tew: Amplification of the ATP-binding cassette 2 transporter gene is functionally linked with enhanced efflux of estramustine in ovarian carcinoma cells. *Cancer Res* 58, 1332-1337 (1998)

64. G. G. Wulf, S. Modlich, N. Inagaki, D. Reinhardt, R. Schroers, F. Griesinger and L. Trumper: ABC transporter ABCA3 is expressed in acute myeloid leukemia blast cells and participates in vesicular transport. *Haematologica* 89, 1395-1397 (2004)

65. T. C. Islam, A. C. Asplund, J. M. Lindvall, L. Nygren, J. Liden, E. Kimby, B. Christensson, C. I. Smith and B. Sander: High level of cannabinoid receptor 1, absence of regulator of G protein signalling 13 and differential expression of Cyclin D1 in mantle cell lymphoma. *Leukemia* 17, 1880-1890 (2003)

66. N. Kartner, J. R. Riordan and V. Ling: Cell surface P-glycoprotein associated with multidrug resistance in mammalian cell lines. *Science* 221, 1285-1288 (1983)

67. L. M. Chan, S. Lowes and B. H. Hirst: The ABCs of drug transport in intestine and liver: efflux proteins limiting drug absorption and bioavailability. *Eur J Pharm Sci* 21, 25-51 (2004)

68. I. Pastan, M. M. Gottesman, K. Ueda, E. Lovelace, A. V. Rutherford and M. C. Willingham: A retrovirus carrying an MDR1 cDNA confers multidrug resistance and polarized expression of P-glycoprotein in MDCK cells. *Proc Natl Acad Sci U S A* 85, 4486-4490 (1988)

69. M. Muller, R. Mayer, U. Hero and D. Keppler: ATP-dependent transport of amphiphilic cations across the hepatocyte canalicular membrane mediated by mdr1 P-glycoprotein. *FEBS Lett* 343, 168-172 (1994)

70. C. J. Matheny, M. W. Lamb, K. R. Brouwer and G. M. Pollack: Pharmacokinetic and pharmacodynamic implications of P-glycoprotein modulation. *Pharmacotherapy* 21, 778-796 (2001)

71. D. de Graaf, R. C. Sharma, E. B. Mechetner, R. T. Schimke and I. B. Roninson: P-glycoprotein confers methotrexate resistance in 3T6 cells with deficient carrier-mediated methotrexate uptake. *Proc Natl Acad Sci U S A* 93, 1238-1242 (1996)

72. H. Zeng, Z. P. Lin and A. C. Sartorelli: Resistance to purine and pyrimidine nucleoside and nucleobase analogs by the human MDR1 transfected murine leukemia cell line L1210/VMDRC.06. *Biochem Pharmacol* 68, 911-921 (2004)

73. P. Wils, V. Phung-Ba, A. Warnery, D. Lechardeur, S. Raeissi, I. J. Hidalgo and D. Scherman: Polarized transport of docetaxel and vinblastine mediated by P-glycoprotein in human intestinal epithelial cell monolayers. *Biochem Pharmacol* 48, 1528-1530 (1994)

74. U. S. Rao, R. L. Fine and G. A. Scarborough: Antiestrogens and steroid hormones: substrates of the human P-glycoprotein. *Biochem Pharmacol* 48, 287-292 (1994)

75. E. Schurr, M. Raymond, J. C. Bell and P. Gros: Characterization of the multidrug resistance protein expressed in cell clones stably transfected with the mouse mdr1 cDNA. *Cancer Res* 49, 2729-2733 (1989)

76. X. P. Zhang, M. K. Ritke, J. C. Yalowich, M. L. Slovak, J. P. Ho, K. I. Collins, T. Annable, R. J. Arceci, F. E. Durr and L. M. Greenberger: P-glycoprotein mediates profound resistance to bisantrene. *Oncol Res* 6, 291-301 (1994)

77. C. B. Hendricks, E. K. Rowinsky, L. B. Grochow, R. C. Donehower and S. H. Kaufmann: Effect of P-glycoprotein expression on the accumulation and cytotoxicity of topotecan (SK&F 104864), a new camptothecin analogue. *Cancer Res* 52, 2268-2278 (1992)

78. F. X. Mahon, F. Belloc, V. Lagarde, C. Chollet, F. Moreau-Gaudry, J. Reiffers, J. M. Goldman and J. V. Melo: MDR1 gene overexpression confers resistance to imatinib mesylate in leukemia cell line models. *Blood* 101, 2368-2373 (2003)

79. S. Hoffmeyer, O. Burk, O. von Richter, H. P. Arnold, J. Brockmoller, A. Johne, I. Cascorbi, T. Gerloff, I. Roots, M. Eichelbaum and U. Brinkmann: Functional polymorphisms of the human multidrug-resistance gene: multiple sequence variations and correlation of one allele with P-glycoprotein expression and activity *in vivo*. *Proc Natl Acad Sci U S A* 97, 3473-3478 (2000)

80. Z. C. Gatmaitan and I. M. Arias: Structure and function of P-glycoprotein in normal liver and small intestine. *Adv Pharmacol* 24, 77-97 (1993)

81. E. G. Schuetz, W. T. Beck and J. D. Schuetz: Modulators and substrates of P-glycoprotein and cytochrome P4503A coordinately up-regulate these proteins in human colon carcinoma cells. *Mol Pharmacol* 49, 311-318 (1996)

82. V. J. Wacher, J. A. Silverman, Y. Zhang and L. Z. Benet: Role of P-glycoprotein and cytochrome P450 3A in limiting oral absorption of peptides and peptidomimetics. *J Pharm Sci* 87, 1322-1330 (1998)

83. S. Ruetz and P. Gros: Phosphatidylcholine translocase: a physiological role for the mdr2 gene. *Cell* 77, 1071-1081 (1994)

84. A. J. Smith, A. van Helvoort, G. van Meer, K. Szabo, E. Welker, G. Szakacs, A. Varadi, B. Sarkadi and P. Borst: MDR3 P-glycoprotein, a phosphatidylcholine translocase, transports several cytotoxic drugs and directly interacts with drugs as judged by interference with nucleotide trapping. *J Biol Chem* 275, 23530-23539 (2000)

85. T. Gerloff, B. Stieger, B. Hagenbuch, J. Madon, L. Landmann, J. Roth, A. F. Hofmann and P. J. Meier: The sister of P-glycoprotein represents the canalicular bile salt export pump of mammalian liver. *J Biol Chem* 273, 10046-10050 (1998)

86. J. A. Byrne, S. S. Strautnieks, G. Mieli-Vergani, C. F. Higgins, K. J. Linton and R. J. Thompson: The human bile salt export pump: characterization of substrate specificity and identification of inhibitors. *Gastroenterology* 123, 1649-1658 (2002)

87. J. Noe, B. Stieger and P. J. Meier: Functional expression of the canalicular bile salt export pump of human liver. *Gastroenterology* 123, 1659-1666 (2002)

88. V. Lecureur, D. Sun, P. Hargrove, E. G. Schuetz, R. B. Kim, L. B. Lan and J. D. Schuetz: Cloning and expression of murine sister of P-glycoprotein reveals a more discriminating transporter than MDR1/P-glycoprotein. *Mol Pharmacol* 57, 24-35 (2000)

89. G. Jedlitschky, I. Leier, U. Buchholz, J. Hummel-Eisenbeiss, B. Burchell and D. Keppler: ATP-dependent transport of bilirubin glucuronides by the multidrug resistance protein MRP1 and its hepatocyte canalicular isoform MRP2. *Biochem J* 327, 305-310 (1997)

90. A. T. Nies and D. Keppler: The apical conjugate efflux pump ABCC2 (MRP2). *Pflugers Arch* 453, 643-659 (2007)

91. H. Akita, H. Suzuki, K. Ito, S. Kinoshita, N. Sato, H. Takikawa and Y. Sugiyama: Characterization of bile acid transport mediated by multidrug resistance associated protein 2 and bile salt export pump. *Biochim Biophys Acta* 1511, 7-16 (2001)

92. D. Keppler, I. Leier and G. Jedlitschky: Transport of glutathione conjugates and glucuronides by the multidrug resistance proteins MRP1 and MRP2. *Biol Chem* 378, 787-791 (1997)

93. P. K. Smitherman, A. J. Townsend, T. E. Kute and C. S. Morrow: Role of multidrug resistance protein 2 (MRP2, ABCC2) in alkylating agent detoxification: MRP2 potentiates glutathione S-transferase A1-1-mediated resistance to chlorambucil cytotoxicity. *J Pharmacol Exp Ther* 308, 260-267 (2004)

94. J. Zhang, Q. Tian, S. Yung Chan, S. Chuen Li, S. Zhou, W. Duan and Y. Z. Zhu: Metabolism and transport of oxazaphosphorines and the clinical implications. *Drug Metab Rev* 37, 611-703 (2005)

95. J. H. Hooijberg, H. J. Broxterman, M. Kool, Y. G. Assaraf, G. J. Peters, P. Noordhuis, R. J. Scheper, P. Borst, H. M. Pinedo and G. Jansen: Antifolate resistance mediated by the multidrug resistance proteins MRP1 and MRP2. *Cancer Res* 59, 2532-2535 (1999)

96. R. Evers, M. Kool, L. van Deemter, H. Janssen, J. Calafat, L. C. Oomen, C. C. Paulusma, R. P. Oude Elferink, F. Baas, A. H. Schinkel and P. Borst: Drug export activity of the human canalicular multispecific organic anion transporter in polarized kidney MDCK cells expressing cMOAT (MRP2) cDNA. *J Clin Invest* 101, 1310-1319 (1998)

97. Y. Cui, J. Konig, J. K. Buchholz, H. Spring, I. Leier and D. Keppler: 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 (1999)

98. X. Y. Chu, Y. Kato and Y. Sugiyama: Multiplicity of biliary excretion mechanisms for irinotecan, CPT-11, and its metabolites in rats. *Cancer Res* 57, 1934-1938 (1997)

99. G. E. Sandusky, K. S. Mintze, S. E. Pratt and A. H. Dantzig: Expression of multidrug resistance-associated protein 2 (MRP2) in normal human tissues and carcinomas using tissue microarrays. *Histopathology* 41, 65-74 (2002)

100. J. Kartenbeck, U. Leuschner, R. Mayer and D. Keppler: Absence of the canalicular isoform of the MRP gene-encoded conjugate export pump from the hepatocytes in Dubin-Johnson syndrome. *Hepatology* 23, 1061-1066 (1996)

101. C. M. Paumi, B. G. Ledford, P. K. Smitherman, A. J. Townsend and C. S. Morrow: Role of multidrug resistance protein 1 (MRP1) and glutathione S-transferase A1-1 in alkylating agent resistance. Kinetics of glutathione conjugate formation and efflux govern differential cellular sensitivity to chlorambucil versus melphalan toxicity. *J Biol Chem* 276, 7952-7956 (2001)

102. C. S. Morrow, C. Peklak-Scott, B. Bishwokarma, T. E. Kute, P. K. Smitherman and A. J. Townsend: Multidrug resistance protein 1 (MRP1, ABCC1) mediates resistance to mitoxantrone via glutathione-dependent drug efflux. *Mol Pharmacol* 69, 1499-1505 (2006)

103. T. Noguchi, X. Q. Ren, S. Aoki, Y. Igarashi, X. F. Che, Y. Nakajima, H. Takahashi, R. Mitsuo, K. Tsujikawa, T. Sumizawa, M. Haraguchi, M. Kobayashi, S. Goto, M. Kanehisa, T. Aikou, S. Akiyama and T. Furukawa: MRP1 mutated in the L0 region transports SN-38 but not leukotriene C4 or estradiol-17 (beta-D-glucuronate). *Biochem Pharmacol* 70, 1056-1065 (2005)

104. C. E. Grant, G. Valdimarsson, D. R. Hipfner, K. C. Almquist, S. P. Cole and R. G. Deeley: Overexpression of multidrug resistance-associated protein (MRP) increases resistance to natural product drugs. *Cancer Res* 54, 357-361 (1994)

105. M. Adachi, J. Sampath, L. B. Lan, D. Sun, P. Hargrove, R. Flatley, A. Tatum, M. Z. Edwards, M. Wezeman, L. Matherly, R. Drake and J. Schuetz: Expression of MRP4 confers resistance to ganciclovir and compromises bystander cell killing. *J Biol Chem* 277, 38998-39004 (2002)

106. Z. S. Chen, K. Lee and G. D. Kruh: Transport of cyclic nucleotides and estradiol 17-beta-D-glucuronide by multidrug resistance protein 4. Resistance to 6-mercaptopurine and 6-thioguanine. *J Biol Chem* 276, 33747-33754 (2001)

107. Z. S. Chen, K. Lee, S. Walther, R. B. Raftogianis, M. Kuwano, H. Zeng and G. D. Kruh: Analysis of methotrexate and folate transport by multidrug resistance protein 4 (ABCC4): MRP4 is a component of the methotrexate efflux system. *Cancer Res* 62, 3144-3150 (2002)

108. Q. Tian, J. Zhang, T. M. Tan, E. Chan, W. Duan, S. Y. Chan, U. A. Boelsterli, P. C. Ho, H. Yang, J. S. Bian, M. Huang, Y. Z. Zhu, W. Xiong, X. Li and S. Zhou: Human multidrug resistance associated protein 4 confers resistance to camptothecins. *Pharm Res* 22, 1837-1853 (2005)

109. N. Zelcer, T. Saeki, G. Reid, J. H. Beijnen and P. Borst: Characterization of drug transport by the human multidrug resistance protein 3 (ABCC3). *J Biol Chem* 276, 46400-46407 (2001)

110. J. Wijnholds, C. A. Mol, L. van Deemter, M. de Haas, G. L. Scheffer, F. Baas, J. H. Beijnen, R. J. Scheper, S. Hatse, E. De Clercq, J. Balzarini and P. Borst: Multidrug-resistance protein 5 is a multispecific organic anion transporter able to transport nucleotide analogs. *Proc Natl Acad Sci U S A* 97, 7476-7481 (2000)

111. J. Madon, B. Hagenbuch, L. Landmann, P. J. Meier and B. Stieger: Transport function and hepatocellular localization of mrp6 in rat liver. *Mol Pharmacol* 57, 634-641 (2000)

112. A. A. Bergen, A. S. Plomp, X. Hu, P. T. de Jong and T. G. Gorgels: ABCC6 and pseudoxanthoma elasticum. *Pflugers Arch* 453, 685-691 (2007)

113. M. G. Belinsky, Z. S. Chen, I. Shchaveleva, H. Zeng and G. D. Kruh: Characterization of the drug resistance and transport properties of multidrug resistance protein 6 (MRP6, ABCC6). *Cancer Res* 62, 6172-6177 (2002)

114. E. Hopper-Borge, Z. S. Chen, I. Shchaveleva, M. G. Belinsky and G. D. Kruh: Analysis of the drug resistance profile of multidrug resistance protein 7 (ABCC10): resistance to docetaxel. *Cancer Res* 64, 4927-4930 (2004)

115. Z. S. Chen, Y. Guo, M. G. Belinsky, E. Kotova and G. D. Kruh: Transport of bile acids, sulfated steroids, estradiol 17-beta-D-glucuronide, and leukotriene C4 by human multidrug resistance protein 8 (ABCC11). *Mol Pharmacol* 67, 545-557 (2005)

116. Y. Guo, E. Kotova, Z. S. Chen, K. Lee, E. Hopper-Borge, M. G. Belinsky and G. D. Kruh: MRP8, ATP-binding cassette C11 (ABCC11), is a cyclic nucleotide efflux pump and a resistance factor for fluoropyrimidines 2',3'-dideoxycytidine and 9'-(2'-phosphonylmethoxyethyl)adenine. *J Biol Chem* 278, 29509-29514 (2003)

117. G. D. Kruh, Y. Guo, E. Hopper-Borge, M. G. Belinsky and Z. S. Chen: ABCC10, ABCC11, and ABCC12. *Pflugers Arch* 453, 675-684 (2007)

118. H. Kusuhara and Y. Sugiyama: ATP-binding cassette, subfamily G (ABCG family). *Pflugers Arch* 453, 735-744 (2007)

119. K. E. Berge, H. Tian, G. A. Graf, L. Yu, N. V. Grishin, J. Schultz, P. Kwiterovich, B. Shan, R. Barnes and H. H. Hobbs: Accumulation of dietary cholesterol in sitosterolemia caused by mutations in adjacent ABC transporters. *Science* 290, 1771-1775 (2000)

120. H. Wittenburg and M. C. Carey: Biliary cholesterol secretion by the twinned sterol half-transporters ABCG5 and ABCG8. *J Clin Invest* 110, 605-609 (2002)

121. T. Litman, M. Brangi, E. Hudson, P. Fetsch, A. Abati, D. D. Ross, K. Miyake, J. H. Resau and S. E. Bates: The multidrug-resistant phenotype associated with overexpression of the new ABC half-transporter, MXR (ABCG2). *J Cell Sci* 113, 2011-2021 (2000)

122. J. Xu, Y. Liu, Y. Yang, S. Bates and J. T. Zhang: Characterization of oligomeric human half-ABC transporter ATP-binding cassette G2. *J Biol Chem* 279, 19781-19789 (2004)

123. L. A. Doyle, W. Yang, L. V. Abruzzo, T. Krogmann, Y. Gao, A. K. Rishi and D. D. Ross: A multidrug resistance transporter from human MCF-7 breast cancer cells. *Proc Natl Acad Sci U S A* 95, 15665-15670 (1998)

124. R. Allikmets, L. M. Schriml, A. Hutchinson, V. Romano-Spica and M. Dean: A human placenta-specific ATP-binding cassette gene (ABCP) on chromosome 4q22 that is involved in multidrug resistance. *Cancer Res* 58, 5337-5339 (1998)

125. M. A. Serrano, R. I. R. Macias, O. Briz, M. J. Monte, A. G. Blazquez, C. Williamson, R. Kubitz and J. J. G. Marin: Expression in human trophoblast and choriocarcinoma cell lines, BeWo, Jeg-3 and JAr of genes involved in the hepatobiliary-like excretory function of the placenta. *Placenta* 28, 107-117 (2007)

126. M. Maliepaard, G. L. Scheffer, I. F. Faneyte, M. A. van Gastelen, A. C. Pijnenborg, A. H. Schinkel, M. J. van de Vijver, R. J. Scheper and J. H. Schellens: Subcellular localization and distribution of the breast cancer resistance protein transporter in normal human tissues. *Cancer Res* 61, 3458-3464 (2001)

127. P. Krishnamurthy, D. D. Ross, T. Nakanishi, K. Bailey-Dell, S. Zhou, K. E. Mercer, B. Sarkadi, B. P. Sorrentino and J. D. Schuetz: The stem cell marker Bcrp/ABCG2 enhances hypoxic cell survival through interactions with heme. *J Biol Chem* 279, 24218-24225 (2004)

128. Y. Imai, S. Asada, S. Tsukahara, E. Ishikawa, T. Tsuruo and Y. Sugimoto: Breast cancer resistance protein exports sulfated estrogens but not free estrogens. *Mol Pharmacol* 64, 610-618 (2003)

129. T. Janvilisri, S. Shahi, H. Venter, L. Balakrishnan and H. W. van Veen: Arginine-482 is not essential for transport of antibiotics, primary bile acids and unconjugated sterols by the human breast cancer resistance protein (ABCG2). *Biochem J* 385, 419-426 (2005)

130. E. L. Volk, K. Rohde, M. Rhee, J. J. McGuire, L. A. Doyle, D. D. Ross and E. Schneider: Methotrexate cross-resistance in a mitoxantrone-selected multidrug-resistant MCF7 breast cancer cell line is attributable to enhanced energy-dependent drug efflux. *Cancer Res* 60, 3514-3521 (2000)

131. E. L. Volk and E. Schneider: Wild-type breast cancer resistance protein (BCRP/ABCG2) is a methotrexate polyglutamate transporter. *Cancer Res* 63, 5538-5543 (2003)

132. R. W. Robey, W. Y. Medina-Perez, K. Nishiyama, T. Lahusen, K. Miyake, T. Litman, A. M. Senderowicz, D. D. Ross and S. E. Bates: Overexpression of the ATP-binding cassette half-transporter, ABCG2 (Mxr/BCrp/ABCP1), in flavopiridol-resistant human breast cancer cells. *Clin Cancer Res* 7, 145-152 (2001)

133. Y. Sugimoto, S. Tsukahara, Y. Imai, Y. Sugimoto, K. Ueda and T. Tsuruo: Reversal of breast cancer resistance protein-mediated drug resistance by estrogen antagonists and agonists. *Mol Cancer Ther* 2, 105-112 (2003)

134. J. D. Allen, R. F. Brinkhuis, J. Wijnholds and A. H. Schinkel: The mouse Bcrp1/Mxr/Abcp gene: amplification and overexpression in cell lines selected for resistance to topotecan, mitoxantrone, or doxorubicin. *Cancer Res* 59, 4237-4241 (1999)

135. J. H. Schellens, M. Maliepaard, R. J. Scheper, G. L. Scheffer, J. W. Jonker, J. W. Smit, J. H. Beijnen and A. H. Schinkel: Transport of topoisomerase I inhibitors by the breast cancer resistance protein. Potential clinical implications. *Ann N Y Acad Sci* 922, 188-194 (2000)

136. M. Maliepaard, M. A. van Gastelen, L. A. de Jong, D. Pluim, R. C. van Waardenburg, M. C. Ruevekamp-Helmers, B. G. Floot and J. H. Schellens: Overexpression of the BCRP/MXR/ABCP gene in a topotecan-selected ovarian tumor cell line. *Cancer Res* 59, 4559-4563 (1999)

137. J. D. Allen, S. C. van Dort, M. Buitelaar, O. van Tellingen and A. H. Schinkel: Mouse breast cancer resistance protein (Bcrp1/Abcg2) mediates etoposide resistance and transport, but etoposide oral availability is limited primarily by P-glycoprotein. *Cancer Res* 63, 1339-1344 (2003)

138. H. Burger, H. van Tol, A. W. Boersma, M. Brok, E. A. Wiemer, G. Stoter and K. Nooter: Imatinib mesylate (STI571) is a substrate for the breast cancer resistance protein (BCRP)/ABCG2 drug pump. *Blood* 104, 2940-2942 (2004)

139. K. Yanase, S. Tsukahara, J. Mitsuhashi and Y. Sugimoto: Functional SNPs of the breast cancer resistance protein-therapeutic effects and inhibitor development. *Cancer Lett* 234, 73-80 (2006)

140. A. Tamura, K. Wakabayashi, Y. Onishi, M. Takeda, Y. Ikegami, S. Sawada, M. Tsuji, Y. Matsuda and T. Ishikawa: Re-evaluation and functional classification of non-synonymous single nucleotide polymorphisms of the human ATP-binding cassette transporter ABCG2. *Cancer Sci* 98, 231-239 (2007)

141. Y. Honjo, C. A. Hrycyna, Q. W. Yan, W. Y. Medina-Perez, R. W. Robey, A. van de Laar, T.

Litman, M. Dean and S. E. Bates: Acquired mutations in the MXR/BCRP/ABCP gene alter substrate specificity in MXR/BCRP/ABCP-overexpressing cells. *Cancer Res* 61, 6635-6639 (2001)

142. Y. Imai, M. Nakane, K. Kage, S. Tsukahara, E. Ishikawa, T. Tsuruo, Y. Miki and Y. Sugimoto: C421A polymorphism in the human breast cancer resistance protein gene is associated with low expression of Q141K protein and low-level drug resistance. *Mol Cancer Ther* 1, 611-616 (2002)

143. S. Mizuarai, N. Aozasa and H. Kotani: Single nucleotide polymorphisms result in impaired membrane localization and reduced atpase activity in multidrug transporter ABCG2. *Int J Cancer* 109, 238-246 (2004)

144. A. Sparreboom, H. Gelderblom, S. Marsh, R. Ahluwalia, R. Obach, P. Principe, C. Twelves, J. Verweij and L. H. McLeod: Diflomotecan pharmacokinetics in relation to ABCG2 421C>A genotype. *Clin Pharmacol Ther* 76, 38-44 (2004)

145. L.A. Doyle, D.D. Ross: Multidrug resistance mediated by the breast cancer resistance protein BCRP (ABCG2). *Oncogene* 22, 7340-7358 (2003)

146. J.M. Ford, W.N. Hait: Pharmacology of drugs that alter multidrug resistance in cancer. *Pharmacol Rev.* 42, 155-199 (1990)

147. W.T. Beck: Mechanisms of multidrug resistance in human tumor cells. The roles of P-glycoprotein, DNA topoisomerase II, and other factors. *Cancer Treat Rev.* 17, 11-20 (1990)

148. W.T. Beck: Modulators of P-glycoprotein-associated multidrug resistance. *Cancer Treat Res.* 57, 151-170 (1991)

149. M. Raderer, W. Scheithauer: Clinicals trials of agents that reverse multidrug resistance. A literature review. *Cancer* 72, 3553-3563 (1993)

150. P.W. Wigler, F.K. Patterson: Inhibition of the multidrug resistance efflux pump. *Biochim Biophys Acta.* 1154, 173-181 (1993)

151. C. Avendano, J.C. Menendez: Inhibitors of multidrug resistance to antitumor agents (MDR). *Curr Med Chem.* 9, 159-193 (2002)

152. M.M. Gottesman, T. Fojo, S.E. Bates: Multidrug resistance in cancer: role of ATP-dependent transporters. *Nat Rev Cancer.* 2, 48-58 (2002)

153. J.M. Meerum Terwogt, J.H. Beijnen, W.W. ten Bokkel Huinink, H. Rosing, J.H. Schellens: Co-administration of cyclosporin enables oral therapy with paclitaxel. *Lancet* 352, 285 (1998)

154. B.L. Lum, S. Kaubisch, A.M. Yahanda, K.M. Adler, L. Jew, M.N. Ehsan, N.A. Brophy, J. Halsey, M.P. Gosland, B.I. Sikic: Alteration of etoposide pharmacokinetics and pharmacodynamics by cyclosporine in a phase I trial to modulate multidrug resistance. *J Clin Oncol.* 10, 1635-1642 (1992)

155. N.L. Bartlett, B.L. Lum, G.A. Fisher, N.A. Brophy, M.N. Ehsan, J. Halsey, B.I. Sikic: Phase I trial of doxorubicin with cyclosporine as a modulator of multidrug resistance. *J Clin Oncol.* 12, 835-842 (1994)

156. S.L. Berg, A. Tolcher, J.A. O'Shaughnessy, A.M. Denicoff, M. Noone, F.P. Ognibene, K.H. Cowan, F.M. Balis: Effect of R-verapamil on the pharmacokinetics of paclitaxel in women with breast cancer. *J Clin Oncol.* 13, 2039-2042 (1995)

157. L. van Zuylen, A. Sparreboom, A. van der Gaast, K. Nooter, F.A. Eskens, E. Brouwer, C.J. Bol, R. de Vries, P.A. Palmer, J. Verweij: Disposition of docetaxel in the presence of P-glycoprotein inhibition by intravenous administration of R101933. *Eur J Cancer.* 38, 1090-1099 (2002)

158. S. Zhang, X. Wang, K. Sagawa, M.E. Morris: Flavonoids chrysin and benzoflavone, potent breast cancer resistance protein inhibitors, have no significant effect on topotecan pharmacokinetics in rats or mdr1a/1b (-/-) mice. *Drug Metab Dispos.* 33, 341-348 (2005)

159. R.M. Wadkins, P.J. Houghton: The role of drug-lipid interactions in the biological activity of modulators of multi-drug resistance. *Biochim Biophys Acta.* 1153, 225-236 (1993)

160. C.W. Sachs, A.R. Safa, S.D. Harrison, R.L. Fine: Partial inhibition of multidrug resistance by safingol is independent of modulation of P-glycoprotein substrate activities and correlated with inhibition of protein kinase C. *J Biol Chem.* 270, 26639-26648 (1995)

161. E. Gupta, A.R. Safa, X. Wang, M.J. Ratain: Pharmacokinetic modulation of irinotecan and metabolites by cyclosporine A. *Cancer Res.* 56, 1309-1314 (1996)

162. M. Horikawa, Y. Kato, Y. Sugiyama: Reduced gastrointestinal toxicity following inhibition of the biliary excretion of irinotecan and its metabolites by probenecid in rats. *Pharm Res.* 19, 1345-1353 (2002)

163. K. Arimori, N. Kuroki, M. Hidaka, T. Iwakiri, K. Yamsaki, M. Okumura, H. Ono, N. Takamura, M. Kikuchi, M. Nakano: Effect of P-glycoprotein modulator, cyclosporin A, on the gastrointestinal excretion of irinotecan and its metabolite SN-38 in rats. *Pharm Res.* 20, 910-917 (2003)

164. K. Ueda, Y. Kato, K. Komatsu, Y. Sugiyama: Inhibition of biliary excretion of methotrexate by probenecid in rats: quantitative prediction of interaction from *in vitro* data. *J Pharmacol Exp Ther.* 297, 1036-1043 (2001)

165. S. Childs, R.L. Yeh, D. Hui, V. Ling: Taxol resistance mediated by transfection of the liver-specific sister gene of P-glycoprotein. *Cancer Res.* 58, 4160-4167 (1998)

166. R.K. Burt, S.S. Thorgeirsson: Coinduction of MDR-1 multidrug-resistance and cytochrome P-450 genes in rat liver by xenobiotics. *J Natl Cancer Inst.* 80, 1383-1386 (1988)

167. T.W. Gant, J.A. Silverman, H.C. Bisgaard, R.K. Burt, P.A. Marino, S.S. Thorgeirsson: Regulation of 2-acetylaminofluorene-and 3-methylcholanthrene--mediated induction of multidrug resistance and cytochrome P450IA gene family expression in primary hepatocyte cultures and rat liver. *Mol Carcinog.* 4, 499-509 (1991)

168. V. Lecureur, A. Guillouzo, O. Fardel: Differential regulation of mdr genes in response to 2-acetylaminofluorene treatment in cultured rat and human hepatocytes. *Carcinogenesis* 17, 1157-1160 (1996)

169. V. Lecureur, J.V. Thottassery, D. Sun, E.G. Schuetz, J. Lahti, G.P. Zambetti, J.D. Schuetz: Mdr1b facilitates p53-mediated cell death and p53 is required for Mdr1b upregulation *in vivo*. *Oncogene* 20, 303-313 (2001)

170. O. Fardel, L. Payen, A. Courtois, V. Lecureur, A. Guillouzo: Induction of multidrug resistance gene expression in rat liver cells in response to acute treatment by the DNA-damaging agent methyl methanesulfonate. *Biochem Biophys Res Commun.* 245, 85-89 (1998)

171. K.N. Furuya, J.V. Thottassery, E.G. Schuetz, M. Sharif, J.D. Schuetz: Bromocriptine transcriptionally activates the multidrug resistance gene (pgp2/mdr1b) by a novel pathway. *J Biol Chem.* 272, 11518-11525 (1997)

172. H.M. Kauffmann, D. Schrenk: Sequence analysis and functional characterization of the 5'-flanking region of the rat multidrug resistance protein 2 (mrp2) gene. *Biochem Biophys Res Commun.* 245, 325-331 (1998)

173. Y. Kiuchi, H. Suzuki, T. Hirohashi, C.A. Tyson, Y. Sugiyama: cDNA cloning and inducible expression of human multidrug resistance associated protein 3 (MRP3). *FEBS Lett.* 433, 149-152 (1998)

174. B. Stockel, J. Konig, A.T. Nies, Y. Cui, M. Brom, D. Keppler: Characterization of the 5'-flanking region of the human multidrug resistance protein 2 (MRP2) gene and its regulation in comparison withthe multidrug resistance protein 3 (MRP3) gene. *Eur J Biochem.* 267, 1347-1358 (2000)

175. K. Ogawa, H. Suzuki, T. Hirohashi, T. Ishikawa, P.J. Meier, K. Hirose, T. Akizawa, M. Yoshioka, Y. Sugiyama: Characterization of inducible nature of MRP3 in rat liver. *Am J Physiol Gastrointest Liver Physiol.* 278, G438-446 (2000)

176. A. Courtois, L. Payen, L. Vernhet, F. Morel, A. Guillouzo, O. Fardel: Differential regulation of canalicular multispecific organic anion transporter (cMOAT) expression by the chemopreventive agent oltipraz in primary rat hepatocytes and in rat liver. *Carcinogenesis* 20, 2327-2330 (1999)

177. A.M. Wielandt, V. Vollrath, M. Manzano, S. Miranda, L. Accatino, J. Chianale: Induction of the multispecific organic anion transporter (cMoat/mrp2) gene and biliary glutathione secretion by the herbicide 2,4,5-trichlorophenoxyacetic acid in the mouse liver. *Biochem J.* 341, 105-111 (1999)

178. H.M. Kauffmann, D. Keppler, T.W. Gant, D. Schrenk: Induction of hepatic mrp2 (cmrp/cmoat) gene expression in nonhuman primates treated with rifampicin or tamoxifen. *Arch Toxicol.* 72, 763-768 (1998)

179. T.W. Gant, J.A. Silverman, S.S. Thorgeirsson: Regulation of P-glycoprotein gene expression in hepatocyte cultures and liver cell lines by a trans-acting transcriptional repressor. *Nucleic Acids Res.* 20, 2841-2846 (1992)

180. H.M. Kauffmann, D. Keppler, J. Kartenbeck, D. Schrenk: Induction of cMrp/cMoat gene expression by cisplatin, 2-acetylaminofluorene, or cycloheximide in rat hepatocytes. *Hepatology* 26, 980-985 (1997)

181. Y.C. Lee, Y.K. Lai: Integrity of intermediate filaments is associated with the development of acquired thermotolerance in 9L rat brain tumor cells. *J Cell Biochem.* 57, 150-162 (1995)

182. G. Conseil, H. Baubichon-Cortay, G. Dayan, J.M. Jault, D. Barron, A. Di Pietro: Flavonoids: a class of modulators with bifunctional interactions at vicinal ATP- and steroid-binding sites on mouse P-glycoprotein. *Proc Natl Acad Sci U S A.* 95, 9831-9836 (1998)

183. E.M. Leslie, Q. Mao, C.J. Oleschuk, R.G. Deeley, S.P. Cole: Modulation of multidrug resistance protein 1 (MRP1/ABCC1) transport and atpase activities by interaction with dietary flavonoids. *Mol Pharmacol.* 59, 1171-1180 (2001)

184. S. Zhang, X. Yang, M.E. Morris: Combined effects of multiple flavonoids on breast cancer resistance protein (ABCG2)-mediated transport. *Pharm Res.* 21, 1263-1273 (2004)

185. S. Zhang, X. Yang, M.E. Morris: Flavonoids are inhibitors of breast cancer resistance protein (ABCG2)-mediated transport. *Mol Pharmacol.* 65, 1208-1216 (2004)

186. G. Scambia, F.O. Ranelletti, P.B. Panici, R. De Vincenzo, G. Bonanno, G. Ferrandina, M. Piantelli, S. Bussa, C. Rumi, M. Cianfriglia, *et al.*: Quercetin potentiates the effect of adriamycin in a multidrug-resistant MCF-7 human breast-cancer cell line: P-glycoprotein as a possible target. *Cancer Chemother Pharmacol.* 34, 459-464 (1994)

187. J.W. Critchfield, C.J. Welsh, J.M. Phang, G.C. Yeh: Modulation of adriamycin accumulation and efflux by flavonoids in HCT-15 colon cells. Activation of P-glycoprotein as a putative mechanism. *Biochem Pharmacol.* 48, 1437-1445 (1994)

188. A.F. Castro, G.A. Altenberg: Inhibition of drug transport by genistein in multidrug-resistant cells expressing P-glycoprotein. *Biochem Pharmacol.* 53, 89-93 (1997)

189. S. Zhang, M.E. Morris: Effect of the flavonoids biochanin A and silymarin on the P-glycoprotein-mediated transport of digoxin and vinblastine in human intestinal Caco-2 cells. *Pharm Res.* 20, 1184-1191 (2003)

190. S. Zhang, M.E. Morris: Effects of the flavonoids biochanin A, morin, phloretin, and silymarin on P-glycoprotein-mediated transport. *J Pharmacol Exp Ther.* 304, 1258-1267 (2003)

191. Y. Mitsunaga, H. Takanaga, H. Matsuo, M. Naito, T. Tsuruo, H. Ohtani, Y. Sawada: Effect of bioflavonoids on vincristine transport across blood-brain barrier. *Eur J Pharmacol.* 395, 193-201 (2000)

192. J.S. Choi, H.K. Choi, S.C. Shin: Enhanced bioavailability of paclitaxel after oral coadministration with flavone in rats. *Int J Pharm.* 275, 165-170 (2004)

193. J.S. Choi, B.W. Jo, Y.C. Kim: Enhanced paclitaxel bioavailability after oral administration of paclitaxel or prodrug to rats pretreated with quercetin. *Eur J Pharm Biopharm.* 57, 313-318 (2004)

194. C.H. Versantvoort, G.J. Schuurhuis, H.M. Pinedo, C.A. Eekman, C.M. Kuiper, J. Lankelma, H.J. Broxterman: Genistein modulates the decreased drug accumulation in non-P-glycoprotein mediated multidrug resistant tumour cells. *Br J Cancer.* 68, 939-946 (1993)

195. C.H. Versantvoort, H.J. Broxterman, J. Lankelma, N. Feller, H.M. Pinedo: Competitive inhibition by genistein and ATP dependence of daunorubicin transport in intact MRP overexpressing human small cell lung cancer cells. *Biochem Pharmacol.* 48, 1129-1136 (1994)

196. H. Nguyen, S. Zhang, M.E. Morris: Effect of flavonoids on MRP1-mediated transport in Panc-1 cells. *J Pharm Sci.* 92, 250-257 (2003)

197. J.J. van Zanden, L. Geraets, H.M. Wortelboer, P.J. van Bladeren, I.M. Rietjens, N.H. Cnubben: Structural requirements for the flavonoid-mediated modulation of glutathione S-transferase P1-1 and GS-X pump activity in MCF7 breast cancer cells. *Biochem Pharmacol.* 67, 1607-1617 (2004)

198. H.C. Cooray, T. Janvilisri, H.W. van Veen, S.B. Hladky, M.A. Barrand: Interaction of the breast cancer resistance protein with plant polyphenols. *Biochem Biophys Res Commun.* 317, 269-275 (2004)

199. Y. Imai, S. Tsukahara, S. Asada, Y. Sugimoto: Phytoestrogens/flavonoids reverse breast cancer resistance protein/ABCG2-mediated multidrug resistance. *Cancer Res.* 64, 4346-4352 (2004)

200. Y. Ji, M.E. Morris: Effect of organic isothiocyanates on breast cancer resistance protein (ABCG2)-mediated transport. *Pharm Res.* 21, 2261-2269 (2004)

201. H. Takanaga, A. Ohnishi, H. Matsuo, Y. Sawada: Inhibition of vinblastine efflux mediated by P-glycoprotein by grapefruit juice components in caco-2 cells. *Biol Pharm Bull.* 21, 1062-1066 (1998)

202. S. Reif, M.C. Nicolson, D. Bisset, M. Reid, C. Kloft, U. Jaehde, H.L. McLeod: Effect of grapefruit juice intake on etoposide bioavailability. *Eur J Clin Pharmacol.* 58, 491-494 (2002)

203. A. Soldner, U. Christians, M. Susanto, V.J. Wacher, J.A. Silverman, L.Z. Benet: Grapefruit juice activates P-glycoprotein-mediated drug transport. *Pharm Res.* 16, 478-485 (1999)

204. X. Wang, A.W. Wolkoff, M.E. Morris: Flavonoids as a novel class of human organic anion-transporting polypeptide OATP1B1 (OATP-C) modulators. *Drug Metab Dispos.* 33, 1666-1672 (2005)

205. A.F. List, C. Spier, J. Greer, S .Wolff, J. Hutter, R. Dorr, S. Salmon, B. Futscher, M. Baier, W. Dalton: Phase I/II trial of cyclosporine as a chemotherapy-resistance modifier in acute leukemia. *J Clin Oncol.* 11, 1652-1660 (1993)

206. G.R. Villanueva, M.E. Mendoza, M.Y. el-Mir, M.J. Monte, M.C. Herrera, J.J. Marin: Effect of bile acids on hepatobiliary transport of cisplatin by perfused rat liver. *Pharmacol Toxicol.* 80, 111-117 (1997)

207. C.P. Yang, S.G. DePinho, L.M. Greenberger, R.J. Arceci, S.B. Horwitz: Progesterone interacts with P-glycoprotein in multidrug-resistant cells and in the endometrium of gravid uterus. *J Biol Chem.* 264, 782-788 (1989)

208. K. Ueda, N. Okamura, M. Hirai, Y. Tanigawara, T. Saeki, N. Kioka, T. Komano, R. Hori: Human P-glycoprotein transports cortisol, aldosterone, and dexamethasone, but not progesterone. *J Biol Chem.* 267, 24248-24252 (1992)

209. X.D. Qian, W.T. Beck: Progesterone photoaffinity labels P-glycoprotein in multidrug-resistant human leukemic lymphoblasts. *J Biol Chem.* 265, 18753-18756 (1990)

210. J. Kirk, S. Houlbrook, N.S. Stuart, I.J. Stratford, A.L. Harris, J. Carmichael: Selective reversal of vinblastine resistance in multidrug-resistant cell lines by tamoxifen, toremifene and their metabolites. *Eur J Cancer.* 29A, 1152-1157 (1993)

211. V. Lecureur, O. Fardel, A. Guillouzo: The antiprogestatin drug RU 486 potentiates doxorubicin cytotoxicity in multidrug resistant cells through inhibition of P-glycoprotein function. *FEBS Lett.* 355, 187-191 (1994)

212. G. Zhou, M.T. Kuo: NF-kappaB-mediated induction of mdr1b expression by insulin in rat hepatoma cells. *J Biol Chem.* 272, 15174-15183 (1997)

213. K.I. Hirsch-Ernst, C. Ziemann, C. Schmitz-Salue, H. Foth, G.F. Kahl: Modulation of P-glycoprotein and mdr1b mRNA expression by growth factors in primary rat hepatocyte culture. *Biochem Biophys Res Commun.* 215, 179-185 (1995)

214. A.L. Russell, C.J. Henderson, G. Smith, C.R. Wolf: Suppression of multi-drug resistance gene expression in the mouse liver by 1,4-bis[2,(3,5-dichloropyridyloxy)] benzene. *Int J Cancer.* 58, 550-554 (1994)

215. A. Courtois, L. Payen, A. Guillouzo, O. Fardel: Up-regulation of multidrug resistance-associated protein 2 (MRP2) expression in rat hepatocytes by dexamethasone. *FEBS Lett.* 459, 381-385 (1999)

216. U Warskulat, R Kubitz, M Wettstein, B Stieger, PJ Meier, D Haussinger: Regulation of bile salt export pump mRNA levels by dexamethasone and osmolarity in cultured rat hepatocytes. *Biol Chem.* 380, 1273-1279 (1999)

217. Y. Liu, F.J. Suchy, J.A. Silverman, M. Vore: Prolactin increases ATP-dependent taurocholate transport in canalicular plasma membrane from rat liver. *Am J Physiol.* 272, G46-53 (1997)

218. J. Cao, L. Huang, Y. Liu, T. Hoffman, B. Stieger, P.J. Meier, M. Vore: Differential regulation of hepatic bile salt and organic anion transporters in pregnant and postpartum rats and the role of prolactin. *Hepatology* 33, 140-147 (2001)

219. J.B. Mitchell, J.A. Cook, W. DeGraff, E. Glatstein, A. Russo: Glutathione modulation in cancer treatment: will it work? Int J Radiat Oncol Biol Phys. 16, 1289-1295 (1989)

220. D.W. Loe, R.G. Deeley, S.P. Cole: Characterization of vincristine transport by the M(r) 190,000 multidrug resistance protein (MRP): evidence for cotransport with reduced glutathione. *Cancer Res.* 58, 5130-5136 (1998)

221. C. C. Huang, M. C. Wu, G. W. Xu, D. Z. Li, H. Cheng, Z. X. Tu, H. Q. Jiang and J. R. Gu: Overexpression of the MDR1 gene and P-glycoprotein in human hepatocellular carcinoma. *J Natl Cancer Inst* 84, 262-264 (1992)

222. E. G. Schuetz, K. N. Furuya and J. D. Schuetz: Interindividual variation in expression of P-glycoprotein in normal human liver and secondary hepatic neoplasms. *J Pharmacol Exp Ther* 275, 1011-1018 (1995)

223. P. M. Chaudhary and I. B. Roninson: Induction of multidrug resistance in human cells by transient exposure to different chemotherapeutic drugs. *J Natl Cancer Inst* 85, 632-639 (1993)

224. D. Schrenk, A. Michalke, T. W. Gant, P. C. Brown, J. A. Silverman and S. S. Thorgeirsson: Multidrug resistance gene expression in rodents and rodent hepatocytes treated with mitoxantrone. *Biochem Pharmacol* 52, 1453-1460 (1996)

225. O. Fardel, V. Lecureur, S. Daval, A. Corlu and A. Guillouzo: Up-regulation of P-glycoprotein expression in rat liver cells by acute doxorubicin treatment. *Eur J Biochem* 246, 186-192 (1997)

226. D. Schrenk, P. R. Baus, N. Ermel, C. Klein, B. Vorderstemann and H. M. Kauffmann: Up-regulation of transporters of the MRP family by drugs and toxins. *Toxicology Letters* 120, 51-57 (2001)

227. C. Ziemann, A. Burkle, G. F. Kahl and K. I. Hirsch-Ernst: Reactive oxygen species participate in mdr1b mRNA and P-glycoprotein overexpression in primary rat hepatocyte cultures. *Carcinogenesis* 20, 407-414 (1999)

228. G. Zhou and M. T. Kuo: Wild-type p53-mediated induction of rat mdr1b expression by the anticancer drug daunorubicin. *J Biol Chem* 273, 15387-15394 (1998)

229. Y. E. Timsit and M. Negishi: CAR and PXR: the xenobiotic-sensing receptors. *Steroids* 72, 231-246 (2007)

230. R. G. Tirona and R. B. Kim: Nuclear receptors and drug disposition gene regulation. *J Pharm Sci* 94, 1169-1186 (2005)

231. H. R. Kast, B. Goodwin, P. T. Tarr, S. A. Jones, A. M. Anisfeld, C. M. Stoltz, P. Tontonoz, S. Kliewer, T. M. Willson and P. A. Edwards: Regulation of multidrug resistance-associated protein 2 (ABCC2) by the nuclear receptors pregnane X receptor, farnesoid X-activated receptor, and constitutive androstane receptor. *J Biol Chem* 277, 2908-2915 (2002)

232. M. Assem, E. G. Schuetz, M. Leggas, D. Sun, K. Yasuda, G. Reid, N. Zelcer, M. Adachi, S. Strom, R. M. Evans, D. D. Moore, P. Borst and J. D. Schuetz: Interactions between hepatic Mrp4 and Sult2a as revealed by the constitutive androstane receptor and Mrp4 knockout mice. *J Biol Chem* 279, 22250-22257 (2004)

233. O. Burk, K. A. Arnold, A. Geick, H. Tegude and M. Eichelbaum: A role for constitutive androstane receptor in the regulation of human intestinal MDR1 expression. *Biol Chem* 386, 503-513 (2005)

234. A. Geick, M. Eichelbaum and O. Burk: Nuclear receptor response elements mediate induction of intestinal MDR1 by rifampin. *J Biol Chem* 276, 14581-14587 (2001)

235. T. W. Synold, I. Dussault and B. M. Forman: The orphan nuclear receptor SXR coordinately regulates drug metabolism and efflux. *Nat Med* 7, 584-590 (2001)

236. J. L. Staudinger, A. Madan, K. M. Carol and A. Parkinson: Regulation of drug transporter gene expression by nuclear receptors. *Drug Metab Dispos* 31, 523-527 (2003)

237. S. Teng, V. Jekerle and M. Piquette-Miller: Induction of ABCC3 (MRP3) by pregnane X receptor activators. *Drug Metab Dispos* 31, 1296-1299 (2003)

238. G.L. Guo, J. Staudinger, K. Ogura and C. D. Klaassen: Induction of rat organic anion transporting polypeptide 2 by pregnenolone-16alpha-carbonitrile is via interaction with pregnane X receptor. *Mol Pharmacol* 61, 832-839 (2002)

239. H. Masuyama, N. Suwaki, Y. Tateishi, H. Nakatsukasa, T. Segawa and Y. Hiramatsu: The pregnane X receptor regulates gene expression in a ligand- and promoter-selective fashion. *Mol Endocrinol* 19, 1170-1180 (2005)

240. E. Schuetz, L. Lan, K. Yasuda, R. Kim, T. A. Kocarek, J. Schuetz and S. Strom: Development of a realtime *in vivo* transcription assay: application reveals pregnane X receptor-mediated induction of CYP3A4 by cancer chemotherapeutic agents. *Mol Pharmacol* 62, 439-445 (2002)

241. S. Donald, R. D. Verschoyle, R. Edwards, D. J. Judah, R. Davies, J. Riley, D. Dinsdale, L. Lopez Lazaro, A. G. Smith, T. W. Gant, P. Greaves and A. J. Gescher: Hepatobiliary damage and changes in hepatic gene expression caused by the antitumor drug ecteinascidin-743 (ET-743) in the female rat. *Cancer Res* 62, 4256-4262 (2002)

242. M. Demeule, M. Brossard, S. Turcotte, A. Regina, J. Jodoin and R. Beliveau: Diallyl disulfide, a chemopreventive agent in garlic, induces multidrug resistance-associated protein 2 expression. *Biochem Biophys Res Commun* 324, 937-945 (2004)

243. C. D. Fisher, L. M. Augustine, J. M. Maher, D. M. Nelson, A. L. Slitt, C. D. Klaassen, L. D. Lehman-McKeeman and N. J. Cherrington: Induction of drug-metabolizing enzymes by garlic and allyl sulfide compounds via activation of constitutive androstane receptor and nuclear factor E2-related factor 2. *Drug Metab Dispos* 35, 995-1000 (2007)

244. M. M. Gottardis, E. D. Bischoff, M. A. Shirley, M. A. Wagoner, W. W. Lamph and R. A. Heyman: Chemoprevention of mammary carcinoma by LGD1069 (Targretin): an RXR-selective ligand. *Cancer Res* 56, 5566-5570 (1996)

245. Y. Wang, R. Yao, A. Maciag, C. J. Grubbs, R. A. Lubet and M. You: Organ-specific expression profiles of rat mammary gland, liver, and lung tissues treated with targretin, 9-cis retinoic acid, and 4-hydroxyphenylretinamide. *Mol Cancer Ther* 5, 1060-1072 (2006)

246. M. Ananthanarayanan, N. Balasubramanian, M. Makishima, D. J. Mangelsdorf and F. J. Suchy: Human bile salt export pump promoter is transactivated by the farnesoid X receptor/bile acid receptor. *J Biol Chem* 276, 28857-28865 (2001)

247. 247. R. Kroker, M. S. Anwer and D. Hegner: A compartmental model for hepatic transport of taurocholic acid in isolated perfused rat liver. *Naunyn Schmiedebergs Arch Pharmacol* 303, 287-293 (1978)

248. P. von Dippe and D. Levy: Expression of the bile acid transport protein during liver development and in hepatoma cells. *J Biol Chem* 265, 5942-5945 (1990)

249. P. Marchegiano, F. Carubbi, C. Tiribelli, S. Amarri, M. Stebel, G.C. Lunazzi, D. Levy and S. Bellentani: Transport of sulfobromophthalein and taurocholate in the HepG2 cell line in relation to the expression of membrane carrier proteins. *Biochem Biophys Res Commun* 183, 1203-1208 (1992)

250. G. A. Kullak-Ublick, U. Beuers and G. Paumgartner: Molecular and functional characterization of bile acid transport in human hepatoblastoma HepG2 cells. *Hepatology* 23, 1053-1060 (1996)

251. Y. Cui, J. Konig, A. T. Nies, M. Pfannschmidt, M. Hergt, W. W. Franke, W. Alt, R. Moll and D. Keppler: Detection of the human organic anion transporters SLC21A6 (OATP2) and SLC21A8 (OATP8) in liver and hepatocellular carcinoma. *Lab Invest* 83, 527-538 (2003)

252. A. Libra, C. Fernetti, V. Lorusso, M. Visigalli, P.L. Anelli, F. Staud, C. Tiribelli and L. Pascolo: Molecular determinants in the transport of a bile acid-derived diagnostic agent in tumoral and nontumoral cell lines of human liver. *J Pharmacol Exp Ther* 319, 809-817 (2006)

253. M. J. Monte, S. Dominguez, M. F. Palomero, R.I.R. Macias and J. J. G. Marin: Further evidence for the usefulness of bile acids as carrier molecules for cytostatic drugs toward liver tumors. *J Hepatol* 31, 521-528 (1999)

254. G. Zollner, M. Wagner, P. Fickert, D. Silbert, A. Fuchsbichler, K. Zatloukal, H. Denk and M. Trauner: Hepatobiliary transporter expression in human hepatocellular carcinoma. *Liver Int* 25, 367-379 (2005)

255. M. R. Ballestero, M. J. Monte, O. Briz, F. Jimenez, F. Gonzalez-San Martin and J. J. G. Marin: Expression of transporters potentially involved in the targeting of cytostatic bile acid derivatives to colon cancer and polyps. *Biochem Pharmacol* 72, 729-738 (2006)

256. S. Vander Borght, L. Libbrecht, H. Blokzijl, K. N. Faber, H. Moshage, R. Aerts, W. Van Steenbergen, P. L. Jansen, V. J. Desmet and T. A. Roskams: Diagnostic and pathogenetic implications of the expression of hepatic transporters in focal lesions occurring in normal liver. *J Pathol* 207, 471-482 (2005)

257. H. Kojima, A. T. Nies, J. Konig, W. Hagmann, H. Spring, M. Uemura, H. Fukui and D. Keppler: Changes in the expression and localization of hepatocellular transporters and radixin in primary biliary cirrhosis. *J Hepatol* 39, 693-702 (2003)

258. G. Zollner, P. Fickert, D. Silbert, A. Fuchsbichler, H. U. Marschall, K. Zatloukal, H. Denk and M. Trauner: Adaptive changes in hepatobiliary transporter expression in primary biliary cirrhosis. *J Hepatol* 38, 717-727 (2003)

259. O. Briz, R. I. R. Macias, M. Vallejo, A. Silva, M. A. Serrano and J. J. G. Marin: Usefulness of liposome-encapsulated cytostatic bile acid derivatives to circumvent chemotherapy resistance of enterohepatic tumors. *Mol Pharmacol* 63, 742-750 (2003)

260. M. G. Larena, M. C. Martinez-Diez, R. I. R. Macias, M. F. Dominguez, M. A. Serrano and J. J. G. Marin: Relationship between tumor cell load and sensitivity to cytostatic effect of two novel platinum-bile acid complexes, Bamet-D3 and Bamet-UD2. *J Drug Target* 10, 397-404 (2002)

261. 261. J. J. G. Marin, M. R. Romero, M. Vallejo and M. J. Monte: Targeting of cytostatic bile acid derivatives toward tumours of the enterohepatic circuit. *Cancer Ther* 3, 57-64 (2005)

262. J. J. G. Marin, M. R. Romero, M. Vallejo, M. J. Perez and O. Briz: Emerging interest of bile acid transporters in Pathophysiology and Pharmacology. *Med Hypoth Res* 2, 425-448 (2005)

263. E. Sievänen: Exploitation of bile acid transport systems in prodrug design. *Molecules* 12, 1-29 (2007)

264. S. Mukhopadhyay and U. Maitra: Chemistry and biology of bile acids. *Curr Sci* 87, 1666-1683 (2004)

265. N. F. H. Ho: Utilizing bile acid carrier mechanisms to enhance liver and small intestine absorption. *Ann NY Acad Sci* 907, 315-329 (1987)

266. D. A. Betebenner, P. L. Carney, A. M. Zimmer and J. M. Kazikiewicz: Hepatobiliary delivery of polyaminopolycarboxylate chelates: Synthesis and characterization of a cholic acid conjugate of EDTA and biodistribution and imaging studies with its indium-111 chelate. *Bioconjug Chem* 2, 117-123 (1991)

267. Z. F. Stephan, E. C. Yurachek, R. Sharif, J. M. Wasvary, R. E. Steele and C. Howes. Reduction of cardiovascular and thyroxine-suppressing activities of L-T3 by liver targeting with cholic acid. *Biochem Pharmacol* 43, 1969-1974 (1992)

268. W. Kramer and G. Wess: Bile acid transport systems as pharmaceutical targets. *Eur J Clin Invest* 26, 715-732 (1996)

269. W. Kramer, F. Girbig, H. Glombik, D. Corsiero, S. Stengelin and C. Weyland: Identification of a ligand-binding site in the Na+/bile acid cotransporting protein from rabbit ileum. *J Biol Chem* 276, 36020-36027 (2001)

270. W. Kramer, G. Wess, G. Schubert, M. Bickel, F. Girbig, U. Gutjahr, S. Kowalewski, K. H. Baringhaus, A. Enhsen, H. Glombik, S. Mullner, G. Neckermann, S. Schulz and E. Petzinger: Liver-specific drug targeting by coupling to bile acids. *J Biol Chem* 267, 18598-18604 (1992)

271. I. M. Eunok, H. C. Yung, P. Kee-Joo, S. Hongsuk, J. Youngeup, K. Kyu-Won, H. Y. Young and D. K. Nam: Novel bile acid derivatives induce apoptosis via a p53-independent pathway in human breast carcinoma cells. *Cancer Letters* 163, 83-93 (2001)

272. F. M. Muggia: Cisplatin update. *Semin Oncol* 18, 1-4 (1991)

273. J. J. Criado, R. I. R. Macias, M. Medarde, M. J. Monte, M. A. Serrano and J. J. G. Marin Synthesis and characterization of the new cytostatic complex cis-diammineplatinum (II)-chlorocholylglycinate. *Bioconjug Chem* 8, 453-458 (1997)

274. J. J. Criado, M. F. Dominguez, M. Medarde, E. R. Fernandez, R. I. R. Macias and J. J. G. Marin: Structural characterization, kinetic studies, and *in vitro* biological activity of new cis-diamminebis-cholylglycinate (O,O') Pt(II) and cis-diamminebis-ursodeoxycholate (O,O') Pt(II) complexes. *Bioconjug Chem* 11, 167-174 (2000)

275. J. Carrasco, J. J. Criado, R. I. R. Macias, J. L. Manzano, J. J. G. Marin, M. Medarde and E. Rodriguez: Structural characterization and cytostatic activity of chlorobischolylglycinatogold(III). *J Inorg Chem* 84, 287-292 (2001)

276. R. Paschke, J. Kalbitz, C. Paetz, M. Luckner, T. Mueller, H.-J. Schmoll, H. Mueller, E. Sorkau and E. Sinn: Cholic acid–carboplatin compounds (CarboChAPt) as models for specific drug delivery: synthesis of novel carboplatin analogous derivatives and comparison of the cytotoxic properties with corresponding cisplatin compounds. *J Inorg Biochem* 94, 335-342 (2003)

277. M. Maeda, N. Takasuka, T. Suga and T. Sasaki: New antitumor platinum(II) complexes with both lipophilicity and water miscibility. *Japan J Cancer Res* 81, 567-569 (1990)

278. R. I. R. Macias, M. J. Monte, M. Y. El-Mir, G. R. Villanueva and J. J. G. Marin: Transport and biotransformation of the new cytostatic complex cis-diammineplatinum(II)-chlorocholylglycinate (Bamet-R2) by the rat liver. *J Lipid Res* 39, 1792-1798 (1998)

279. M. G. Larena, M. C. Martinez-Diez, M. J. Monte, M. F. Dominguez, M. J. Pascual and J. J. G. Marin: Liver organotropism and biotransformation of a novel platinum-ursodeoxycholate derivative, Bamet-UD2, with enhanced antitumor activity. *J Drug Target* 9, 185-200 (2001)

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