A critical review on modulators of Multidrug Resistance Protein 1 in cancer cells

Vivian Osei Poku and Surtaj Hussain Iram

1 Department of Chemistry and Biochemistry, South Dakota State University, Brookings, SD, United States of America
2 American University of Iraq, Sulaimaniya, Sulaimani, KRG, Iraq

ABSTRACT

Multidrug resistance protein 1 (MRP1/ABCC1) is an ATP-dependent efflux transporter, and responsible for the transport of a broad spectrum of xenobiotics, toxins, and physiological substrates across the plasma membrane. As an efflux pump, it plays a significant role in the absorption and disposition of drugs including anticancer drugs, antivirals, antimalarials, and antibiotics and their metabolites across physiological barriers in cells. MRP1 is also known to aid in the regulation of several physiological processes such as redox homeostasis, steroid metabolism, and tissue defense. However, its overexpression has been reported to be a key clinical marker associated with multidrug resistance (MDR) of several types of cancers including lung cancer, childhood neuroblastoma, breast and prostate carcinomas, often resulting in a higher risk of treatment failure and shortened survival rates in cancer patients. Aside MDR, overexpression of MRP1 is also implicated in the development of neurodegenerative and cardiovascular diseases. Due to the cellular importance of MRP1, the identification and biochemical/molecular characterization of modulators of MRP1 activity and expression levels are of key interest to cancer research and beyond. This review primarily aims at highlighting the physiological and pharmacological importance of MRP1, known MRP1 modulators, current challenges encountered, and the potential benefits of conducting further research on the MRP1 transporter.

INTRODUCTION

The advancement of combinatorial chemotherapy regimen to cure cancers has resulted in improved survival rates and quality of life for most cancer patients. Despite the success of this treatment modality, multidrug resistance (MDR) has limited its effectiveness. MDR is a phenomenon in which tumor cells develop resistance to a variety of drugs (Lehnert, 1996). Currently, three mechanisms are known to cause MDR; decreased uptake of water-soluble drugs, cellular changes in cells that reduce the ability of cytotoxic drugs to kill cells, and increased energy-dependent efflux of hydrophobic drugs (Szakács et al., 2006). The pharmacological goal of chemotherapeutic agents is to deliver as much active drug as possible to the molecular target in cancer cells to cause enough cellular damage...
leading to cell death. However, the reduction in drug accumulation (low dose) is one of the factors that decrease the amount of active drug components reaching tumor cells (Molinski et al., 2017; Osa-Andrews et al., 2018). Recent advancement in clinical research has led to the use of nanoparticles (NPs)-based delivery systems as drug carriers allows controlled drug release from the matrix, improves drug bioavailability as well as provides versatile routes of drug administration (Gelperina et al., 2005). Nonetheless, due to the potential toxicity and insufficient transportation of these NPs, only a few have been accepted for clinical treatment (Yin et al., 2018). Aside these drawbacks, recent studies have revealed that ATP-binding cassette (ABC) transporters may be involved in the efflux and detoxification of some of these NPs thereby decreasing their efficacy (Al-Hajaj et al., 2011; Chen et al., 2016; Tian et al., 2019; Yuan et al., 2021).

The ABC transporters are a superfamily of transporters that were initially identified in studies related to nutrient uptake in bacteria in the 1970s (Berger & Heppel, 1974). P-glycoprotein was the first ABC transporter to be discovered in 1973 (George, 2016). Following subsequent studies, this superfamily of transporters was recognized to be ubiquitous and involved in diverse biochemical and physiological processes (Hyde et al., 1990).

The ATP-binding cassette (ABC) transporters play a pivotal role in the removal of hydrophobic drugs across plasma membranes. Unfortunately, some of these therapeutic agents are substrates of these transporters hence they are effluxed out leading to a decrease in intracellular drug concentration. This goes a long way to affect the bioavailability of the drug as well as their therapeutic impact on tumor cells.

Various proteins in the ABC superfamily are reported to be involved in the absorption, excretion, and distribution of drugs in normal cells (Szakács et al., 2008), however, in cancer cells (where these transporters are overexpressed), therapeutic agents administered are challenged by the efflux activity of these membrane-bound efflux pumps mainly ABC transporters like P-glycoprotein (P-gp) and Multidrug Resistance Protein 1(MRP1) since they serve as the first line of defense (Gottesman, Pastan & Ambudkar, 1996; Kool et al., 1997).

MDR remains a major impediment to the treatment of cancers as its resulting ineffectiveness of the drug treatment is responsible for a larger percentage (about 90%) of cancer-related deaths (Li et al., 2008; Longley & Johnston, 2005; Si et al., 2019), hence the role of ABC transporters which contribute to MDR cannot be overlooked.

SURVEY METHODOLOGY

An extensive survey of existing literature was conducted using Google Scholar and PubMed to analyze the role of ABC transporters in the development of MDR in cancer, with a focus on the MRP1 transporter, its modulators, challenges that limit their efficacy as well as potential strategies that can be explored in overcoming MRP1 mediated MDR in cancer cells. Scientific literature reviewed was not refined by journal type, authors, or publishing date. We also considered results from our previous research works on the MRP1 transporter and cross-referenced published literature to identify other appropriate and related resources.
OVERVIEW OF ATP-BINDING CASSETTE TRANSPORTERS

Membrane transport proteins are one of the essential proteins that aid in the transfer of several classes of molecules in and out of cells. Ion channels, transporters, aquaporins, and ATP-powered pumps are the four different types of membrane transport proteins (Vasiliou, Vasiliou & Nebert, 2009). ATP-powered pumps are ATPases that move ions or small molecules across a membrane via active transport (movement of molecules against a concentration or electrochemical gradient) using ATP hydrolysis as the energy source (Lodish et al., 2000b). Examples of ATP powered pumps include the Na⁺/K⁺ ATPase in the plasma membrane which maintains the Na⁺ and K⁺ gradients typically in animal cells, Ca²⁺ ATPases that function to pump Ca²⁺ ions out of the cytosol into the external medium or the lumen of the sarcoplasmic reticulum (SR) of muscle cells (Lodish et al., 2000a; Toyoshima, 2009), and ATP binding cassette (ABC) pumps; a large, ubiquitous, and diverse superfamily of transporters. ABC transporters are a type of ATP-binding cassette pumps that are encoded by ABC genes (Verrier et al., 2008), and play a critical role in the transport of a wide class of molecules including sugars, amino acids, peptides, metabolites, xenobiotics, and toxins across both the extra- and intracellular membrane (Broehan et al., 2013; Labbé, Caveney & Donly, 2011). The ABC transporters are the largest protein transporter superfamily present in all organisms and are categorized into importers or exporters depending on the direction of the transport relative to the cytoplasm (Dassa & Bouige, 2001). In prokaryotes, they act as both efflux and influx proteins extruding drugs and toxins out of the cell and transporting nutrients into the cell respectively, however, they can also act solely as efflux transporters in eukaryotes, where they play a key role in protecting cells from toxins (Videira, Reis & Brito, 2014). In plants, ABC transporters aid in the transfer of molecules like lipids, metals among others (Verrier et al., 2008).

Structural analysis of ABC transporters reveals an ABC transport core unit that comprises two nucleotide-binding domains (NBDs) and several hydrophobic α-helices forming the membrane-spanning domains (MSDs). The NBDs consist of highly conserved regions or motifs such as the ABC signature motif, the Walker A and Walker B sequences, the H and Q loops (Vasiliou, Vasiliou & Nebert, 2009). The NBDs facilitate ATP hydrolysis to generate energy whereas MSDs on the other hand use the energy generated by the NBDs to catalyze substrate recognition and translocation across the lipid membrane (Vasiliou, Vasiliou & Nebert, 2009).

In humans, 49 ABC genes are currently known and have been grouped into various subfamilies based on their amino acid sequence and protein domains. This classification includes ABCA (12 members), ABCB (11 members), ABCC (13 members), ABCD (4 members), ABCE (1 member), ABCF (3 members), ABCG (5 members) (Auner et al., 2010; Dean, Hamon & Chimini, 2001). ABC transporters are expressed in several organs such as the liver, kidney, adrenal, lungs, intestines, and at various pharmacological sanctuary sites like the blood–brain barrier and the blood-testis barrier (El-Awady et al., 2017), where they are reported to function as channels, receptors, and transporters (Vasiliou, Vasiliou & Nebert, 2009). ABC transporters like P-gp, MRP1, and BCRP have also been reported to play a pivotal role in drug metabolism specifically in phase O and phase III
In phase O, they are reported to regulate the entry and extrusion (exit) of drugs before they reach their pharmacological target, resulting in a significant decrease in the intracellular concentration of the drugs, hence affecting their pharmacological efficacy. In phase III, ABC transporters are known to aid in the complete elimination of metabolized molecules. Due to the important role of ABC transporters in drug metabolism, their overexpression has been associated with the multidrug resistance (MDR) phenomenon, a major opponent to the success of the chemotherapeutic regime. Like most essential proteins, studies have revealed that mutation in ABC transporters genes can lead to crucial and recessive disorders including neurological disorders, retinal degeneration, cystic fibrosis among others (Dean, Hamon & Chimini, 2001).

**THE ABCC SUBFAMILY**

The ABCC subfamily comprises thirteen members. This family of transporters is primarily associated with the export of amphiphilic anions which includes conjugates of lipophilic compounds with glutathione (Keppler, Jedlitschky & Leier, 1998; König et al., 1999). However, recent studies have shown that ABCC6 and ABCC12 are likely not involved in the transport of drugs since their pharmacological and physiological function in cancer chemotherapy remains unclear (Chen & Tiwari, 2011; Sharom et al., 2011). The ABCC subfamily can be categorized into multidrug resistance protein subgroup (MRPs), sulfonylurea receptor subgroup (SURs), and Cystic fibrosis transmembrane conductance regulator (CFTR). The MRP subgroup is made up of nine members, with the SUR subgroup consisting of two members as listed in Table 1.

Members of the MRPs subgroup can also be classified into two main groups based on their predicted topology: the short and long MRPs (Deeley, Westlake & Cole, 2006). The short MRPs are characterized by four domains which include two membrane-spanning domains (MSD1 and MSD2, which are made up of six transmembrane helices), and two nucleotide-binding domains (NBD1 and NBD2). MRPs classified as short proteins include ABCC4/MRP4, ABCC5/MRP5, ABCC11/MRP8, and ABCC12/MRP9 (Chen & Tiwari, 2011). The long MRPs on the other hand are characterized by an extra poorly conserved NH$_2$–terminal region and also predicted to have a third membrane-spanning domain in addition to the two other membrane-spanning domains known as the MSD0 (Deeley, Westlake & Cole, 2006). The MSD0 contains five domain helices. Members of this group include ABCC1/MRP1, ABCC2/MRP2, ABCC3/MRP3, ABCC6/MRP6, ABCC10/MRP7 (Iram & Cole, 2011; Iram & Cole, 2012).

**MULTIDRUG RESISTANCE PROTEIN 1 (MRP1/ABCC1)**

Studies by Cole and her colleagues identified the overexpression of a transporter gene in a multidrug-resistant human lung cancer cell line (H69AR) which did not overexpress P-glycoprotein (P-gp) (a well-studied ABC transporter) (Cole et al., 1992). This transporter was later found to be an ABC efflux pump, known as MRP1 (Cole et al., 1994). MRP1 belongs to the ABCC subfamily of ABC transporters and is encoded by the gene ABCC1. MRP1/ABCC1 is a 1531 amino acid plasma membrane protein with a molecular mass of
Table 1  Summary of members of the ABCC subfamily.

| ABCC subgroup | Symbol | Alternative name | Tissue localization | References |
|---------------|--------|------------------|---------------------|------------|
| MRPs          | ABCC1  | MRP1             | Ubiquitous (lungs, kidney, placenta, blood–brain barrier) | Flens et al. (1996), Kourti et al. (2007) |
|               | ABCC2  | MRP2             | Canicular membrane of hepatocytes. Apical membrane of proximal renal tubule endothelial cells | Kool et al. (1997), Sekine, Miyazaki & Endou (2006) |
|               | ABCC3  | MRP3             | Liver, colon, intestine, adrenal gland | Kool et al. (1997) |
|               | ABCC4  | MRP4             | Prostate, testis, ovary, intestine, pancreas, lung | Borst et al. (1999), Gottesman & Ambudkar (2001) |
|               | ABCC5  | MRP5             | Skeletal muscle, brain, heart | McAleer et al. (1999) |
|               | ABCC6  | MRP6             | Liver, kidney | Gillet, Effert & Remacle (2007) |
|               | ABCC10 | MRP7             | Liver, peripheral blood cells, intestines | Bleasby et al. (2006) |
|               | ABCC11 | MRP8             | Breast, lung, colon, prostate, ovary | Yabuuchi et al. (2001) |
|               | ABCC12 | MRP9             | Testicular germ cells, sperms | Ono et al. (2007) |
| SURs          | ABCC8  | SUR1             | Neuronal cells, pancreatic B-cells | Gribble et al. (1998) |
|               | ABCC9  | SUR2             | SUR 2A - cardiac and skeletal muscle, SUR 2B—vascular smooth muscle | Davis-Taber et al. (2000), Isomoto et al. (1996) |
| CFTR          | ABCC7  | MRP10            | Apical membrane of epithelial cells in exocrine glands | Vankeerberghen, Cappens & Cassiman (2002) |

190 kDa (Cole et al., 1994). MRP1 is expressed at normal levels in the lungs, kidney, placenta, and heart (Flens et al., 1996; Kourti et al., 2007), with lower expression levels observed in the colon, brain, small intestine, and peripheral blood mononuclear cells (Flens et al., 1996; Jaramillo et al., 2018; Kourti et al., 2007). High expression levels of the transporter are observed in cells at various pharmacological sanctuary sites like the blood–brain barrier, blood-testis barrier, and in the basolateral membrane of polarized cells (Bakos et al., 2000; Lu, Pokharel & Bebawy, 2015) as well as in cells with high proliferative status such as the reactive type II pneumocytes in the alveoli of the lungs (Bréchet et al., 1998). MRP1 as an ATP-dependent efflux transporter plays a major role in transporting broad spectrum substrates. These substrates include organic anions, metalloids (sodium arsenite, potassium antimonite), toxicants ( aflatoxin B1, methoxychlor) folic acids, bilirubin, vitamins, glutathione and glucuronide-conjugates of steroids, leukotrienes, and prostaglandins B12 (Cole, 2014; Deeley, Westlake & Cole, 2006; Munoz et al., 2007). Some endobiotics transported by MRP1 include doxorubicin, vincristine, paclitaxel, ritonavir, irinotecan, methotrexate, saquinavir (Munoz et al., 2007). Due to the ability of MRP1 to transport drugs from different drug families irrespective of their molecular target, structure, and mode of action, (Poku, 2021) MRP1 has been reported to regulate the absorption and
disposition of drugs as well as their metabolites across cells (Osa-Andrews et al., 2018, Poku, 2021; Takenaka, Itoh & Fujiwara, 2013).

Structural analysis of MRP1 reveals two nucleotide-binding domains (NBDs) and two membrane-spanning domains (MSDs) similar to most ABC transporters. The MSDs consist of membrane-spanning domains (MSD1 and MSD2) with each MSD-containing six transmembrane α-helices (Dawson & Locher, 2007). Also, MRP1 possesses a distinct third N-terminal transmembrane spanning domain (MSD0) which comprises five transmembrane spanning helices (Sharom et al., 2011) as shown in Fig. 1.

Studies have shown that MSD0 facilitates interactions between the transporter and other protein partners (Koch et al., 2004). Structural studies have revealed that when MRP1 is not bound to any substrate or ATP, it assumes an inward-facing conformation, while the NBDs are widely separated, and the translocation pathway remains continuous with the cytoplasm (Johnson & Chen, 2017). On the other hand, the MSDs get closer to form a high affinity substrate binding site at which a substrate binds to the transporter, this results in the NBDs moving closer to each other and aligning themselves for dimerization (Johnson & Chen, 2017; Johnson & Chen, 2018). Upon ATP binding, dimerization of the NBDs and rearrangement of the MSDs occurs leading to the outward-facing conformation of the transporter (Johnson & Chen, 2018; Payen et al., 2003). Sequentially, the residues forming the substrate-binding site tend to be pulled apart as the extracellular ends of the helices of the MSDs peel outward leading to a significant reduction in the binding affinity of the substrate to the transporter, the substrate is then released into the extracellular space (Johnson & Chen, 2018).

Recently, several retrospective analyses of chemotherapy results have reported high expression profiles of MRP1 aside from Breast Cancer Resistance Protein (BCRP) and P-gp (Roundhill & Burchill, 2013). Yet, MRP1 is severely understudied although the role of ABC transporters like BCRP and P-gp has been well explored. Interestingly, recent evidence has associated overexpression of MRP1 with a higher incidence of treatment failure, resulting in cancer relapse and poor survival rates in some cancer patients (Greaves et al., 2012).
Moreover, the overexpression of MRP1 has also been implicated in the development of multidrug resistance in several cancers like ovarian, lung, breast, pancreatic, kidney carcinomas, and in malignant melanoma (Barrand et al., 1993; Larkin et al., 2004; Li et al., 2009; O’Driscoll et al., 2007; Tong et al., 2019; Walsh et al., 2010; Walsh et al., 2009). Studies by Yang and colleagues also reported elevated expression of MRP1 in colorectal adenocarcinoma and its involvement in the infiltration and metastasis of colorectal adenocarcinoma (Yang, Song & Zhou, 2019). The US food and drug administration (FDA) recommendation in 2017 strongly heralded the need to screen drugs at the clinical trial stages for their likely interaction with MDR proteins such as BCRP and P-gp (FDA, 2020). This recommendation excluded MRP1 even though it is considered as one of the transporters whose overexpression highly influences MDR. Moreover, in addition to anticancer agents, the overexpression of MRP1 has also been reported to reduce the efficacy of various antivirals (saquinavir, zidovudine, ritonavir), antimalarials (berberine), and antibiotics (benzylpenicillin, difloxacin, grepafloxacin) (Deeley & Cole, 2006; Eilers, Roy & Mondal, 2008; Perloff et al., 2001a; Peterson et al., 2017; Shitan et al., 2007; Zhao et al., 2019). MRP1 is also reported to be a major player in the regulation of several physiological processes like redox homeostasis, steroid metabolism, tissue defense, and the etiology of neurodegenerative and cardiovascular diseases (Ballatori et al., 2009a; Ballatori et al., 2009b; Cole, 2014; Krohn et al., 2011; Leslie, Deeley & Cole, 2005; Long, Li & Cui, 2011; Park et al., 2011; Sivils, Gonzalez & Bain, 2010). Considering the unique role of MRP1 and its contribution to MDR, it is expedient to gain more insight into the pharmacological essence of this transporter by profiling for its biochemical interactions with both new and promising drug targets.

**ROLE OF MODULATORS IN CHEMOTHERAPY**

ABC transporters play a critical role in maintaining normal cellular function and cellular balance. However, cancer cells in their intelligence take advantage of the efflux activity of these transporters by overexpressing these transporters to reduce the antitumor effect of chemotherapeutic drugs. As a result, overexpression of ABC transporters contributes to multidrug resistance in several tumor cells. Studies have shown that ABC transporters like MRP1 play a critical role in the development of multidrug resistance, thus it is of great clinical interest to identify pathways or drugs that can reduce the negative impact due to their overexpression. One feasible approach is to completely shut off these efflux pumps, however, due to their pivotal role in maintaining physiological homeostasis, this option may negatively influence normal cellular balance and function (Sivils, Gonzalez & Bain, 2010; Wijnholds et al., 1997). For instance, studies by Sivils and his colleagues reported reduced testicular steroid hormone levels and alterations in steroid biosynthetic enzymes in MRP1 knock-out mice (Sivils, Gonzalez & Bain, 2010). Likewise, impairment of inflammatory stimulus was observed in mice which had MRP1 knock-out although mice exhibited increased sensitivity to anticancer drugs and were fertile and viable (Wijnholds et al., 1997).

An alternative methodology is to modulate the activity of these transporters in cancer cells via biochemical modulation. In this approach, pathways can be biochemically modified
by therapeutic agents to enhance the therapeutic potency of anticancer drugs as well as reduce their toxic side effects to normal cells (Fuertes, Alonso & Pérez, 2003; Peters & Van Groeningen, 1991).

Based on the interactions between ABC transporters and various ligands, ligands can be classified as inhibitors, substrates, activators, and inducers. Inhibitors are described as compounds or molecules that either bind directly or indirectly to the transporter to impair its transport activity. Substrates are compounds that are effluxed by the transporter. Activators are compounds that act to enhance the transport activity of these transporters by facilitating conformational changes that promote the transport or efflux of a substrate. Inducers are rather ligands that upregulate the protein expression levels of the transporter (Wessler et al., 2013). By applying biochemical modulation, the activity of the transporter can be inhibited by a modulator without necessarily influencing the normal balance of healthy cells hence, the need to identify modulators is very essential in cancer treatment. Therapeutic agents that inhibit the activity of the transporter could be used together with other anticancer drugs that are known substrates of the transporter. Thus, the identified inhibitor would dampen the efflux activity of the transporter, allowing the anticancer drug to be bioavailable at the appropriate intracellular concentration to exert its effect on the cancer cells. Consequently, enhancing combinatorial drug therapy (use of two or more pharmacologic agents administered separately or in a fixed dose as a single formulation) in cancer patients. Studies on the role of modulators in chemotherapy have also revealed that modulators also possess the side benefit of enhancing oral bioavailability and improving penetration of drugs that are transported by these transporters in tissues (Shukla, Ohnuma & Ambudkar, 2011).

MODULATORS OF MRP1

MRP1 transporters were discovered several years after the initial characterization of P-gp transporters. Thus, although studies have uncovered and characterized several modulators of P-gp (Luna-Tortós, Fedrowitz & Löscher, 2008; Maitrejean et al., 2000; Starling et al., 1997), there is very little scientific information on modulators of MRP1. For this reason, the goal of identifying modulators of MRP1 is of key interest to oncology research and great clinical value in addressing multidrug resistance. To provide further insight on MRP1 modulators, three main approaches were explored: derivatives of phytochemicals, miRNA-based therapy, and tyrosine kinase inhibitors (TKIs), and other small molecules.

Phytochemicals and their derivatives

Natural compounds like phytochemicals have been established as compounds that can modulate MRP1 activity. Polyphenols like curcumin, tetrahydroxycurcumin, and bioflavonoids like apigenin, quercetin have been reported to have a significant effect on the transport activity of MRP1 (Li et al., 2010; Morris & Zhang, 2006). Studies have shown that some bioflavonoids can interact with the NBDs of MRP1, hence they can regulate the ability of MRP1 to bind and hydrolyze ATP thereby modulating its transport activity (Morris & Zhang, 2006). Some bioflavonoids are also able to act as competitive substrates whereas others may serve as non-substrate inhibitors. The activities of such natural compounds...
on MRP1 may be impacted by the presence of glutathione (GSH). For instance, apigenin can enhance MRP1 mediated transport of GSH by six-folds when an increase greater than 10-fold occurs in the apparent $K_m$ (GSH) (Leslie, Deeley & Cole, 2003). Other flavonoids like morin, chalcone, silymarin, phloretin, genistein, biochanin A, and kaempferol have also been reported to inhibit MRP1-mediated drug transport (Nguyen, Zhang & Morris, 2003). 3B-Acetyl Tormentic Acid (3ATA), a triterpene isolated from Cecropia lyratiliba also inhibits the transport activity of MRP1 by downregulating the total intracellular glutathione (GSH) levels, thereby reducing the activity of glutathione-s-transferase (GST) the enzyme responsible for glutathione conjugation of xenobiotics. Thus, 3ATA was able to sensitize human small cell lung carcinoma cells (GLC4/ADR) to antineoplastic drugs, doxorubicin, and vincristine (Da Graça Rocha et al., 2014). Furthermore, recent studies revealed that the active metabolite of vitamin D3, calcitriol (1,25-dihydroxyvitamin), and its analog, calcipotriol can modulate the activity of MRP1 by specifically inhibiting its transport activity (Tan et al., 2018). Vincristine, a vinca alkaloid isolated from the periwinkle plant (Catharanthus roseus (L.) G. Don), used in the treatment of leukemia, lymphoma, rhabdomyosarcoma (soft tissue tumors), neuroblastoma (cancer that forms in nerve tissue) and other carcinomas is also reported to be a well-known substrate of MRP1. Similar activity is also demonstrated by the plant alkaloid and topoisomerase II inhibitor, etoposide (Pommier et al., 2010).

**miRNA and antibody-based therapy**

The use of microRNAs (miRNAs) as a therapeutic tool has gained a lot of interest in recent years. It has also gained a lot of attention in the field of oncology where aside from acting as biomarkers for fingerprinting various diseases (circulating miRNAs), they are also reported to play key roles in the development of therapeutic interventions with the added advantage of silencing a wide spectrum of genes (Yeung & Jeang, 2011). Thus, they are reported to have a higher potency in controlling the growth and spread of cancer as compared to the traditional cancer treatment approach. With advancements in miRNA-based therapy for the identification of modulators of MRP1, miR-326 has been reported to down-regulate MRP1 mRNA (Liang et al., 2010). Although the miRNA-based therapies are promising, one major drawback encountered is translating this tool from the bench side to the clinic. Studies have also shown that antibodies like QCRL2, QCRL3 that bind to an MRP1-NBD1 based epitope, and QCRL4 that binds to an MRP1-NBD2 based epitope also exert some inhibitory effect on MRP1 (Cole, 2014; Hipfner et al., 1999). MRP1 Internal Binding 6 (MIB6), an MRP1 specific antibody, inhibited MRP1 ATPase activity in MRP1 overexpressing human small lung cancer cells (Hooijberg et al., 1999a). Recent studies by Li and colleagues also showed that Mab-IR700, an anti-MRP1 antibody exhibit a strong modulatory effect in H69AR cells (Li et al., 2021). However, unlike P-gp where several monoclonal antibodies have been developed against its extracellular epitopes and can inhibit its efflux activity, most MRP1-specific antibodies detect linear epitopes of the transporter but are not able to inhibit its transport activity. This may be because MRP1 is characterized by short extracellular loops, thus little of the transporter is accessible on the cell surface (Cole, 2014). This phenomenon makes developing antibodies targeting
extracellular epitopes of MRP1 very challenging and as such, it has been a major hindrance to the antibody-based therapy regime.

**Tyrosine kinase inhibitors and other small molecules**

TKIs are small molecules that are designed to inhibit the upregulated activity of various tyrosine kinase receptors involved in cancer (Broekman, Giovannetti & Peters, 2011). TKIs function by hindering the ATP-binding pocket of its tyrosine kinase targets (Cole, 2014). TKIs such as Ibrutinib have been reported to inhibit the activity of MRPI (Zhang et al., 2014). Rapamycin, an inhibitor of the intracellular serine/threonine kinase (mTOR) that is implicated in the phosphoinositide 3-kinase (PI3K)/Akt signaling pathway, also inhibits the transport activity of MRPI (Brown et al., 1994; Peterson et al., 2017; Sui, Wang & Li, 2008). A Calcein-based high content screening of a unique library of clinically tested anticancer drugs (Z’-factor of 0.63) showed that first-generation rapalogs (analogs of rapamycin)- deforolimus, everolimus, and temsirolimus (ester analog of rapamycin) inhibit the transport activity of MRPI in small cell lung cancer cells (H69AR), thereby increasing the sensitivity of these cells to vincristine treatment (Peterson et al., 2017). Except for everolimus which had been reported to decrease the MRPI expression levels in cisplatin-resistant gastric cancer cells (Ying et al., 2014), the effect of other identified inhibitors on the protein expression levels of the MRPI transporter remains to be elucidated. Other inhibitors that were identified in the study included ESI -09 (a specific inhibitor of EPAC (exchange protein directly activated by Camp), tipifarnib (farnesyltransferase inhibitor), TAK-733 (selective mitogen-activated protein kinase allosteric site inhibitor), HS-173, YM201636 (PI3K inhibitors), AZD1208, CX-6258 (Pan-Pim kinase inhibitors). In another molecular screening conducted in which doxorubicin was used as the fluorescent reporter (average Z’ factor = 0.58) identified several inhibitors (drugs that showed inhibition ≥ 40%) of MRPI from a unique library of drugs (Sampson et al., 2019). These inhibitors include GSK2126458, MK-2206, mifepristone (progesterone and glucocorticoid hormone antagonist), celecoxib (selective cyclooxygenase inhibitor), and doramapimod (p38 MAPK inhibitor), including two novel inhibitors: alisertib (a second-generation Aurora kinase A and B inhibitor) and amuvatinib (an oral multi-kinase inhibitor of RAD51 and PDGFRa). Other inhibitors identified included flavopiridol, NVP-BSK805, saracatinib, OSI-420, LY294002, rosiglitazone, alvespimycin, LY2228820, GSK461364, GW4064, and afatinib. In another study, small molecules such as the human immunodeficiency virus type 1 (HIV-1) protease inhibitor, ritonavir has also been reported to induce expression levels of MRPI in a human intestinal cell line, LS-180 V (Perloff et al., 2001b). Drugs such as rifampicin, dexamethasone, vinblastine, and sulindac have also been reported to be inducers of MRPI (Nishimura et al., 2008; Schrenk et al., 2001; Tatebe, Sinicrope & Kuo, 2002). Sulindac and its primary metabolites; sulindac sulfide and sulindac sulfone have also been reported to inhibit MRPI in some studies (Davies & Watson, 1997; Stride, Cole & Delee, 1999). Substrates of MRPI include anthracyclines such as doxorubicin, daunorubicin, epirubicin, mitoxantrone, flutamide, and methotrexate (Barrand et al., 1993; Cole et al., 1994; Grant et al., 1994; Hooijberg et al., 1999b; Renes et al., 1999). Cyclosporin A, a known modulator of P-gp has also been reported to modulate MRPI (Qadir et al., 2005) by inhibiting its efflux
activity. Disulfiram, a drug used in the treatment of alcoholism, can also act as a modulator of MRP1 by preventing or inhibiting ATP hydrolysis (Sauna et al., 2004). Structural-activity relationship (SAR) studies of indomethacin mediated MRP1 inhibition identified several analogues of indomethacin that inhibited MRP1 activity (Touhey et al., 2002). Likewise, SAR analysis of sulfur-containing verapamil derivatives revealed that the more lipophilic dithiane compounds were more potent in inhibiting MRP1 mediated leukotriene C₄ (LTC₄) transport in the presence of GSH (Loe et al., 2000). Findings from these studies indicate that variations in the molecular structure of current modulators may provide a promising base for the development of potent inhibitors of MRP1. Other inhibitors of MRP1 transport activity include organic acids such as sulfinpyrazone, benz bromarone, probenecid (Hollo et al., 1996), the LTC₄ analog MK571 and S-decylglutathione (Eckford & Sharom, 2009; Gekeler et al., 1995). MK571 is one of the standard modulators used in the inhibition of MRP1.

With regards to activators of MRP1, few molecules such as glutathione analogs, specific flavonoids, phenothiazines, some purine, and pyrrolopyrimidines analogs have been reported (Schmitt, 2017; Schmitt, Stefan & Wiese, 2017). This limited number highlights the fact that current knowledge on modulators of MRP1 is still narrow, and therefore calls for more research to be conducted with regards to identifying more potent modulators of MRP1. Surprisingly, most studies investigated the impact of these therapeutic agents on MRP1 activity, but scarcely considered how they affect the protein and gene expression levels of MRP1.

**CONCLUSION AND FUTURE DIRECTIONS**

There is no doubt that the discovery of modulators of MRP1 has had several potential therapeutic benefits especially for patients with drug-resistant tumors. Although most identified modulators of MRP1 have had significant effects on regulating its transport activity, one of the key challenges encountered in clinical trials has been the efficacy and safety of these modulators. Some dreadful side effects and elevated levels of patient toxicities have been reported due to adverse pharmacokinetic interactions with administered anticancer drugs. For instance, the coadministration of cyclosporin A and etoposide to a patient with acute T-lymphocytic leukemia in relapse resulted in progressive hyperbilirubinemia and mental confusion (Kloke & Osieka, 1985). Although toxicity remains a major setback to the success of these modulators, a dose-escalating, single arm, prospective, open label, non-randomized phase I trial of epirubicin in combination with escalating oral doses of sulindac (0–800 mg) in patients with advanced cancer showed that a 600mg oral “pre-dose of sulindac can be combined with a fixed dose of 75mg/m² epirubicin without affecting the conventional toxicity and pharmacokinetics of the anthracycline chemotherapy drug (O’Connor et al., 2007). Moreover, studies by Burkhart and colleagues revealed that reversan, an inhibitor of MRP1 when used in combination with vincristine and etoposide increased tumor sensitivity to these conventional drugs in murine models of neuroblastoma (syngeneic and human xenografts) with no increase in toxicity levels of these conventional agents (Burkhart et al., 2009). Thus, there is the need for further
research to be conducted to identify more non-toxic modulators of MRP1 that can be utilized in clinical treatment of MRP1 associated cancers.

Another setback encountered is the genetic variation of single-nucleotide polymorphisms (SNPs). SNPs are defined as polymorphisms that are caused by a point mutation (changes in a DNA base sequence in which a nucleotide may be deleted, added, or substituted) resulting in varying alleles having alternative bases at a precise position of nucleotide within a locus (Jin et al., 2016). The difference in drug absorption, distribution, and elimination has been observed due to single-nucleotide polymorphisms in proteins responsible for drug transport (Kroetz, Yee & Giacomini, 2010). These variations have resulted in differences in toxicity levels and drug response in several patients, including patients with MRP1 SNPs. For instance, MRP1/ABCC1 SNPs in patients with non-Hodgkin’s lymphoma and pediatric cancers resulted in cardiotoxicity in response to anthracycline treatment (Visscher et al., 2012; Wojnowski et al., 2005). Considering the negative impact of SNPs, it would be necessary to adequately genotype clinical trial subjects. Aside from these current challenges, a critical review of literature on modulators of MRP1 reveals that although most MRP1 modulators could influence transporter activity, little is known about their impact on the gene and protein expression levels of the MRP1. Thus, further research must be conducted to investigate how current and future therapeutic agents that interact with MRP1 may affect its protein and gene expression levels. The identification of agents that modulate the expression levels of MRP1 could provide new insights toward the development of more specific and effective therapeutic tools as well as deepen our understanding of the pharmacological and physiological nature of MRP1 transporters.

ACKNOWLEDGEMENTS
The authors are grateful to the Department of Chemistry and Biochemistry, South Dakota State University for their general support.

ADDITIONAL INFORMATION AND DECLARATIONS

Funding
There was no funding for this article.

Competing Interests
The authors declare there are no competing interests.

Author Contributions
• Vivian Osei Poku conceived and designed the experiments, performed the experiments, analyzed the data, prepared figures and/or tables, authored or reviewed drafts of the paper, and approved the final draft.
• Surtaj H. Iram conceived and designed the experiments, analyzed the data, authored or reviewed drafts of the paper, and approved the final draft.
Data Availability
The following information was supplied regarding data availability:
This is a review article and there is no raw data.

REFERENCES

Al-Hajaj NA, Moquin A, Neibert KD, Soliman GM, Winnik FM, Maysinger D. 2011. Short ligands affect modes of QD uptake and elimination in human cells. *Acs Nano* 5:4909–4918 DOI 10.1021/nn201009w.

Auner V, Sehouli J, Oskay-Oezcelik G, Horvat R, Speiser P, Zeillinger R. 2010. ABC transporter gene expression in benign and malignant ovarian tissue. *Gynecologic Oncology* 117:198–201 DOI 10.1016/j.ygyno.2009.10.077.

Bakos E, Evers R, Calenda G, Tusnády GE, Szakács G, Váradi A, Sarkadi B. 2000. Characterization of the amino-terminal regions in the human multidrug resistance protein (MRP1). *Journal of Cell Science* 113:4451–4461 DOI 10.1242/jcs.113.24.4451.

Ballatori N, Krance SM, Marchan R, Hammond CL. 2009a. Plasma membrane glutathione transporters and their roles in cell physiology and pathophysiology. *Molecular Aspects of Medicine* 30:13–28 DOI 10.1016/j.mam.2008.08.004.

Ballatori N, Krance SM, Notenboom S, Shi S, Tieu K, Hammond CL. 2009b. Glutathione dysregulation and the etiology and progression of human diseases.

Barrand M, Rhodes T, Center M, Twentyman P. 1993. Chemosensitisation and drug accumulation effects of cyclosporin A, PSC-833 and verapamil in human MDR large cell lung cancer cells expressing a 190k membrane protein distinct from P-glycoprotein. *European Journal of Cancer* 29:408–415 DOI 10.1016/0959-8049(93)90397-X.

Berger EA, Heppel LA. 1974. Different mechanisms of energy coupling for the shock-sensitive and shock-resistant amino acid permeases of Escherichia coli. *Journal of Biological Chemistry* 249:7747–7755 DOI 10.1016/S0021-9258(19)42031-0.

Bleasby K, Castle J, Roberts C, Cheng C, Bailey W, Sina J, Kulkarni A, Hafezy M, Evers R, Johnson J. 2006. Expression profiles of 50 xenobiotic transporter genes in humans and pre-clinical species: a resource for investigations into drug disposition. *Xenobiotica* 36:963–988 DOI 10.1080/00498250600861751.

Borst P, Evers R, Kool M, Wijnholds J. 1999. The multidrug resistance protein family. *Biochimica Et Biophysica Acta (BBA)-Biomembranes* 1461:347–357 DOI 10.1016/S0005-2736(99)00167-4.

Bréchot J-M, Hurbain I, Fajac A, Daty N, Bernaudin J-F. 1998. Different pattern of MRP localization in ciliated and basal cells from human bronchial epithelium. *Journal of Histochemistry & Cytochemistry* 46:513–517 DOI 10.1177/002215549804604011.

Broehan G, Kroeger T, Lorenzen M, Merzendorfer H. 2013. Functional analysis of the ATP-binding cassette (ABC) transporter gene family of Tribolium castaneum. *BMC Genomics* 14:6 DOI 10.1186/1471-2164-14-6.

Broekman F, Giovannetti E, Peters GJ. 2011. Tyrosine kinase inhibitors: multi-targeted or single-targeted? *World J Clin Oncol* 2:80–93 DOI 10.5306/wjco.v2.i2.80.
Brown EJ, Albers MW, Shin TB, Keith CT, Lane WS, Schreiber SL. 1994. A mammalian protein targeted by G1-arresting rapamycin–receptor complex. *Nature* 369:756–758 DOI 10.1038/369756a0.

Burkhart CA, Watt F, Murray J, Pajic M, Prokvolit A, Xue C, Flemming C, Smith J, Purmal A, Isachenko N. 2009. Small molecule MRP1 inhibitor reversan increases the therapeutic index of chemotherapy in mouse model of neuroblastoma. *Cancer Research* 69:6573 DOI 10.1158/0008-5472.CAN-09-1075.

Chen ZS, Tiwari AK. 2011. Multidrug resistance proteins (MRPs/ABCCs) in cancer chemotherapy and genetic diseases. *The FEBS Journal* 278:3226–3245 DOI 10.1111/j.1742-4658.2011.08235.x.

Chen M, Yin H, Bai P, Miao P, Deng X, Xu Y, Hu J, Yin J. 2016. ABC transporters affect the elimination and toxicity of CdTe quantum dots in liver and kidney cells. *Toxicology and Applied Pharmacology* 303:11–20 DOI 10.1016/j.taap.2016.04.017.

Cole SP. 2014. Targeting multidrug resistance protein 1 (MRP1, ABCC1): past, present, and future. *Annual Review of Pharmacology and Toxicology* 54:95–117 DOI 10.1146/annurev-pharmtox-011613-135959.

Cole S, Bhardwaj G, Gerlach J, Mackie J, Grant C, Almquist K, Stewart A, Kurz E, Duncan A, Deeley RG. 1992. Overexpression of a transporter gene in a multidrug-resistant human lung cancer cell line. *Science* 258:1650–1654 DOI 10.1126/science.1360704.

Cole SP, Sparks KE, Fraser K, Loe DW, Grant CE, Wilson GM, Deeley RG. 1994. Pharmacological characterization of multidrug resistant MRP-transfected human tumor cells. *Cancer Research* 54:5902–5910.

Da Graça Rocha G, Oliveira RR, Kaplan MAC, Gattass CR. 2014. 3β-Acetyl tormentic acid reverts MRP1/ABCC1 mediated cancer resistance through modulation of intracellular levels of GSH and inhibition of GST activity. *European Journal of Pharmacology* 741:140–149 DOI 10.1016/j.ejphar.2014.07.054.

Dassa E, Bouige P. 2001. The ABC of ABCs: a phylogenetic and functional classification of ABC systems in living organisms. *Research in Microbiology* 152:211–229 DOI 10.1016/S0923-2508(01)01194-9.

Davies NM, Watson MS. 1997. Clinical pharmacokinetics of sulindac. *Clinical Pharmacokinetics* 32:437–459 DOI 10.2165/00003088-199732060-00002.

Davis–Taber R, Choi W, Feng J, Hoogenboom L, McNally T, Kroeger P, Shieh CC, Simmer R, Brioni JD, Sullivan JP. 2000. Molecular characterization of human SUR2-containing KATP channels. *Gene* 256:261–270 DOI 10.1016/S0378-1119(00)00338-3.

Dawson RJ, Locher KP. 2007. Structure of the multidrug ABC transporter Sav1866 from Staphylococcus aureus in complex with AMP-PNP. *FEBS Letters* 581:935–938 DOI 10.1016/j.febslet.2007.01.073.

Dean M, Hamon Y, Chimini G. 2001. The human ATP-binding cassette (ABC) transporter superfamily. *Journal of Lipid Research* 42:1007–1017 DOI 10.1016/S0022-2275(20)31588-1.
Deeley RG, Cole SP. 2006. Substrate recognition and transport by multidrug resistance protein 1 (ABCC1). FEBS Letters 580:1103–1111 DOI 10.1016/j.febslet.2005.12.036.

Deeley RG, Westlake C, Cole SP. 2006. Transmembrane transport of endo- and xenobiotics by mammalian ATP-binding cassette multidrug resistance proteins. Physiological Reviews 86:849–899 DOI 10.1152/physrev.00035.2005.

Eckford PD, Sharom FJ. 2009. ABC efflux pump-based resistance to chemotherapy drugs. Chemical Reviews 109:2989–3011 DOI 10.1021/cr9000226.

Eilers M, Roy U, Mondal D. 2008. MRP (ABCC) transporters-mediated efflux of anti-HIV drugs, saquinavir and zidovudine, from human endothelial cells. Experimental Biology and Medicine 233:1149–1160 DOI 10.3181/0802-RM-59.

El-Awady R, Saleh E, Hashim A, Soliman N, Dallah A, Elrasheed A, Elakraa G. 2017. The role of eukaryotic and prokaryotic ABC transporter family in failure of chemotherapy. Frontiers in Pharmacology 7:535.

Flens MJ, Zaman G, Van der Valk P, Izquierdo MA, Schroeijers AB, Scheffer GL, Van Der Groep P, De Haas M, Meijer C, Scheper RJ. 1996. Tissue distribution of the multidrug resistance protein. The American Journal of Pathology 148:1237.

Food and Drug Administration. 2020. In vitro drug interaction studiesâ€”cytochrome P450 enzyme-and transporter-mediated drug interactions guidance for industry, US Department of Health and Human Services. Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD.

Fuertes MA, Alonso C, Pérez JM. 2003. Biochemical modulation of cisplatin mechanisms of action: enhancement of antitumor activity and circumvention of drug resistance. Chemical Reviews 103:645–662 DOI 10.1021/cr020010d.

Gekeler V, Ise W, Sanders KH, Ulrich WR, Beck J. 1995. The leukotriene LTD4 receptor antagonist MK571 specifically modulates MRP associated multidrug resistance. Biochemical and Biophysical Research Communications 208:345–352 DOI 10.1006/bbrc.1995.1344.

Gelperina S, Kisich K, Iseman MD, Heifets L. 2005. The potential advantages of nanoparticle drug delivery systems in chemotherapy of tuberculosis. American Journal of Respiratory and Critical Care Medicine 172:1487–1490 DOI 10.1164/rccm.200504-613PP.

George AM. 2016. ABC transporters-40 years on. Amsterdam, The Netherland: Springer.

Gillet J-P, Efferth T, Remacle J. 2007. Chemotherapy-induced resistance by ATP-binding cassette transporter genes. Biochimica Et Biophysica Acta (BBA)-Reviews on Cancer 1775:237–262 DOI 10.1016/j.bbcan.2007.05.002.

Gottesman MM, Ambudkar SV. 2001. Overview: ABC transporters and human disease. Journal of Bioenergetics and Biomembranes 33:453–458 DOI 10.1023/A:1012866803188.

Gottesman MM, Pastan I, Ambudkar SV. 1996. P-glycoprotein and multidrug resistance. Current opinion in genetics & development 6:610–617.

Grant CE, Valdimarsson G, Hipfner DR, Almquist KC, Cole SP, Deeley RG. 1994. Overexpression of multidrug resistance-associated protein (MRP) increases resistance to natural product drugs. Cancer Research 54:357–361.
Greaves W, Xiao L, Sanchez-Espiridion B, Kunkalla K, Dave KS, Liang CS, Singh RR, Younes A, Medeiros LJ, Vega F. 2012. Detection of ABCC1 expression in classical Hodgkin lymphoma is associated with increased risk of treatment failure using standard chemotherapy protocols. Journal of Hematology & Oncology 5:47 DOI 10.1186/1756-8722-5-47.

Gribble FM, Tucker SJ, Seino S, Ashcroft FM. 1998. Tissue specificity of sulfonylureas: studies on cloned cardiac and beta-cell K (ATP) channels. Diabetes 47:1412–1418 DOI 10.2337/diabetes.47.9.1412.

Hipfner DR, Mao Q, Qiu W, Leslie EM, Gao M, Deeley RG, Cole SP. 1999. Monoclonal antibodies that inhibit the transport function of the 190-kDa multidrug resistance protein, MRP localization of their epitopes to the nucleotide-binding domains of the protein. Journal of Biological Chemistry 274:15420–15426 DOI 10.1074/jbc.274.22.15420.

Hollo Z, Homolya L, Hegedus T, Sarkadi B. 1996. Transport properties of the multidrug resistance-associated protein (MRP) in human tumour cells. FEBS Letters 383:99–104 DOI 10.1016/0014-5793(96)00237-2.

Hooijberg JH, Broxterman HJ, Kool M, Assaraf YG, Peters GJ, Noordhuis P, Scheper RJ, Borst P, Pinedo HM, Jansen G. 1999b. Antifolate resistance mediated by the multidrug resistance proteins MRP1 and MRP2. Cancer Research 59:2532–2535.

Hooijberg J, Broxterman H, Scheffer G, Vrasdonk C, Heijn M, De Jong M, Scheper R, Lankelma J, Pinedo H. 1999a. Potent interaction of flavopiridol with MRP1. British Journal of Cancer 81:269–276 DOI 10.1038/sj.bjc.6690687.

Hyde SC, Emsley P, Hartshorn MJ, Mimmack MM, Gileadi U, Pearce SR, Gallagher MP, Gill DR, Hubbard RE, Higgins CF. 1990. Structural model of ATP-binding proteing associated with cystic fibrosis, multidrug resistance and bacterial transport. Nature 346:362–365 DOI 10.1038/346362a0.

Iram SH, Cole SP. 2011. Expression and function of human MRP1 (ABCC1) is dependent on amino acids in cytoplasmic loop 5 and its interface with nucleotide binding domain 2. Journal of Biological Chemistry 286:7202–7213 DOI 10.1074/jbc.M110.166959.

Iram SH, Cole SP. 2012. Mutation of Glu521 or Glu535 in cytoplasmic loop 5 causes differential misfolding in multiple domains of multidrug and organic anion transporter MRP1 (ABCC1). Journal of Biological Chemistry 287:7543–7555 DOI 10.1074/jbc.M111.310409.

Isomoto S, Kondo C, Yamada M, Matsumoto S, Higashiguchi O, Horio Y, Matsuzawa Y, Kurachi Y. 1996. A novel sulfonylurea receptor forms with BIR (Kir6, 2) a smooth muscle type ATP-sensitive K+ channel. Journal of Biological Chemistry 271:24321–24324 DOI 10.1074/jbc.271.40.24321.

Jaramillo AC, Saig FA, Cloos J, Jansen G, Peters GJ. 2018. How to overcome ATP-binding cassette drug efflux transporter-mediated drug resistance? Cancer Drug Resistance 1:6–29 DOI 10.20517/cdr.2018.02.

Jin Y, Liu S, Yuan Z, Yang Y, Tan S, Liu Z. 2016. Catfish genomic studies: progress and perspectives. Genomics in Aquaculture 73–104.
Johnson ZL, Chen J. 2017. Structural basis of substrate recognition by the multidrug resistance protein MRP1. Cell 168:1075–1085 DOI 10.1016/j.cell.2017.01.041.

Johnson ZL, Chen J. 2018. ATP binding enables substrate release from multidrug resistance protein 1. Cell 172:81–89 DOI 10.1016/j.cell.2017.12.005.

Keppler D, Jedlitschky G, Leier I. 1998. [45] Transport function and substrate specificity of multidrug resistance protein. Methods in Enzymology 292:607–616.

Kloke O, Osieka R. 1985. Interaction of cyclosporin A with antineoplastic agents. Klinische Wochenschrift 63:1081–1082 DOI 10.1007/BF01739677.

Koch J, Guntrum R, Heintke S, Kyritsis C, Tampé R. 2004. Functional dissection of the transmembrane domains of the transporter associated with antigen processing (TAP). Journal of Biological Chemistry 279:10142–10147 DOI 10.1074/jbc.M312816200.

König J, Nies AT, Cui Y, Leier I, Keppler D. 1999. Conjugate export pumps of the multidrug resistance protein (MRP) family: localization, substrate specificity, and MRP2-mediated drug resistance. Biochimica Et Biophysica Acta (BBA)-Biomembranes 1461:377–394 DOI 10.1016/S0005-2736(99)00169-8.

Kool M, De Haas M, Scheffer GL, Scheper RJ, Van Eijk MJ, Juijn JA, Baas F, Borst P. 1997. Analysis of expression of cMOAT (MRP2), MRP3, MRP4, and MRP5, homologues of the multidrug resistance-associated protein gene (MRP1), in human cancer cell lines. Cancer Research 57:3537–3547.

Kourtí M, Vavatsi N, Gombakis N, Sidi V, Tzimagiorgis G, Papageorgiou T, Koliouskas D, Athanassiadou F. 2007. Expression of multidrug resistance 1 (MDR1), multidrug resistance-related protein 1 (MRP1), lung resistance protein (LRP), and breast cancer resistance protein (BCRP) genes and clinical outcome in childhood acute lymphoblastic leukemia. International Journal of Hematology 86:166–173 DOI 10.1532/IJH97.E0624.

Kroetz DL, Yee SW, Giacomini KM. 2010. The pharmacogenomics of membrane transporters project: research at the interface of genomics and transporter pharmacology. Clinical Pharmacology & Therapeutics 87:109–116 DOI 10.1038/clpt.2009.226.

Krohn M, Lange C, Hofrichter J, Scheffler K, Stenzel J, Steffen J, Schumacher T, Brüning T, Plath A-S, Alfen F. 2011. Cerebral amyloid-β proteostasis is regulated by the membrane transport protein ABCC1 in mice. The Journal of Clinical Investigation 121:3924–3931 DOI 10.1172/JCI57867.

Labbé R, Caveney S, Donly C. 2011. Genetic analysis of the xenobiotic resistance-associated ABC gene subfamilies of the Lepidoptera. Insect Molecular Biology 20:243–256 DOI 10.1111/j.1365-2583.2010.01064.x.

Larkin A, O’Driscoll L, Kennedy S, Purcell R, Moran E, Crown J, Parkinson M, Clynes M. 2004. Investigation of MRP-1 protein and MDR-1 P-glycoprotein expression in invasive breast cancer: a prognostic study. International Journal of Cancer 112:286–294 DOI 10.1002/ijc.20369.

Lehnert M. 1996. Clinical multidrug resistance in cancer: a multifactorial problem. European Journal of Cancer 32:912–920 DOI 10.1016/0959-8049(96)00069-X.
Leslie EM, Deeley RG, Cole SP. 2003. Bioflavonoid stimulation of glutathione transport by the 190-kDa multidrug resistance protein 1 (MRP1). *Drug Metabolism and Disposition: The Biological Fate of Chemicals* 31:11–15 DOI 10.1124/dmd.31.1.11.

Leslie EM, Deeley RG, Cole SP. 2005. Multidrug resistance proteins: role of P-glycoprotein, MRP1, MRP2, and BCRP (ABCG2) in tissue defense. *Toxicology and Applied Pharmacology* 204:216–237 DOI 10.1016/j.taap.2004.10.012.

Li J, Li Z-N, Du Y-J, Li X-Q, Bao Q-L, Chen P. 2009. Expression of MRP1, BCRP, LRP, and ERCC1 in advanced non–small-cell lung cancer: correlation with response to chemotherapy and survival. *Clinical Lung Cancer* 10:414–421 DOI 10.3816/CLC.2009.n.078.

Li X, Lewis MT, Huang J, Gutierrez C, Wu M-F, Hilsenbeck SG, Pavlick A, Zhang X, Channess GC. 2008. Intrinsic resistance of tumorigenic breast cancer cells to chemotherapy. *Journal of the National Cancer Institute* 100:672–679 DOI 10.1093/jnci/djn123.

Li F, Mao C, Yeh S, Sun Y, Xin J, Shi Q, Ming X. 2021. MRP1-targeted near infrared photoimmunotherapy for drug resistant small cell lung cancer. *International Journal of Pharmaceutics* 604:120760 DOI 10.1016/j.ijpharm.2021.120760.

Li Y, Revalde JL, Reid G, Paxton JW. 2010. Interactions of dietary phytochemicals with ABC transporters: possible implications for drug disposition and multidrug resistance in cancer. *Drug Metabolism Reviews* 42:590–611 DOI 10.3109/03602531003758690.

Liang Z, Wu H, Xia J, Li Y, Zhang Y, Huang K, Wagar N, Yoon Y, Cho HT, Scala S. 2010. Involvement of miR-326 in chemotherapy resistance of breast cancer through modulating expression of multidrug resistance-associated protein 1. *Biochemical Pharmacology* 79:817–824 DOI 10.1016/j.bcp.2009.10.017.

Lodish H, Berk A, Zipursky SL, Matsudaira P, Baltimore D, Darnell J. 2000a. Active transport by ATP-powered pumps. In: *Molecular cell biology 4th edition*. New York: WH Freeman.

Lodish H, Berk A, Zipursky SL, Matsudaira P, Baltimore D, Darnell J. 2000b. Electron transport and oxidative phosphorylation. In: *Molecular cell biology 4th edition*. New York: WH Freeman.

Loe DW, Oleschuk CJ, Deeley RG, Cole SP. 2000. Structure–activity studies of verapamil analogs that modulate transport of leukotriene C4 and reduced glutathione by multidrug resistance protein MRP1. *Biochemical and Biophysical Research Communications* 275:795–803 DOI 10.1006/bbrc.2000.3384.

Long Y, Li Q, Cui Z. 2011. Molecular analysis and heavy metal detoxification of ABCC1/MPR1 in zebrafish. *Molecular Biology Reports* 38:1703–1711 DOI 10.1007/s11033-010-0283-z.

Longley D, Johnston P. 2005. Molecular mechanisms of drug resistance. *The Journal of Pathology: A Journal of the Pathological Society of Great Britain and Ireland* 205:275–292 DOI 10.1002/path.1706.

Lu JF, Pokharel D, Bebawy M. 2015. MRP1 and its role in anticancer drug resistance. *Drug Metabolism Reviews* 47:406–419 DOI 10.3109/03602532.2015.1105253.
Luna-Tortós C, Fedrowitz M, Löscher W. 2008. Several major antiepileptic drugs are substrates for human P-glycoprotein. *Neuropharmacology* 55:1364–1375 DOI 10.1016/j.neuropharm.2008.08.032.

Maîtrejean M, Comte G, Barron D, Kirat KEI, Conseil G, Di Pietro A. 2000. The flavonolignan silybin and its hemisynthetic derivatives, a novel series of potential modulators of P-glycoprotein. *Bioorganic & Medicinal Chemistry Letters* 10:157–160 DOI 10.1016/S0960-894X(99)00636-8.

McAleer MA, Breen MA, White NL, Matthews N. 1999. pABC11 (also known as MOAT-C and MRP5), a member of the ABC family of proteins, has anion transporter activity but does not confer multidrug resistance when overexpressed in human embryonic kidney 293 cells. *Journal of Biological Chemistry* 274:23541–23548 DOI 10.1074/jbc.274.33.23541.

Molinski SV, Bozóky Z, Iram SH, Ahmadi S. 2017. Biophysical approaches facilitate computational drug discovery for ATP-binding cassette proteins. *International Journal of Medicinal Chemistry* 2017.

Morris ME, Zhang S. 2006. Flavonoid-drug interactions: effects of flavonoids on ABC transporters. *Life Sciences* 78:2116–2130 DOI 10.1016/j.lfs.2005.12.003.

Muñoz M, Henderson M, Haber M, Norris M. 2007. Role of the MRP1/ABCC1 multidrug transporter protein in cancer. *IUBMB Life* 59:752–757 DOI 10.1080/15216540701736285.

Nguyen H, Zhang S, Morris ME. 2003. Effect of flavonoids on MRP1-mediated transport in Panc-1 cells. *Journal of Pharmaceutical Sciences* 92:250–257 DOI 10.1002/jps.10283.

Nishimura M, Koeda A, Morikawa H, Satoh T, Narimatsu S, Naito S. 2008. Comparison of inducibility of multidrug resistance (MDR)1, multidrug resistance-associated protein (MRP)1, and MRP2 mRNAs by prototypical microsomal enzyme inducers in primary cultures of human and cynomolgus monkey hepatocytes. *Biological and Pharmaceutical Bulletin* 31:2068–2072 DOI 10.1248/bpb.31.2068.

O'Connor R, O'Leary M, Ballot J, Collins C, Kinsella P, Mager D, Arnold R, O'Driscoll L, Larkin A, Kennedy S. 2007. A phase I clinical and pharmacokinetic study of the multi-drug resistance protein-1 (MRP-1) inhibitor sulindac in combination with epirubicin in patients with advanced cancer. *Cancer Chemotherapy and Pharmacology* 59:79–87.

O'Driscoll L, Walsh N, Larkin A, Ballot J, Ooi W, Gullo G, O’connor R, Clynnes M, Crown J, Kennedy S. 2007. MDR1/P-glycoprotein and MRP-1 drug efﬂux pumps in pancreatic carcinoma. *Anticancer Research* 27:2115–2120.

Ono N, Van der Heijden I, Scheffer GI, Vande Wetering K, Van Deemter E, De Haas M, Boeke A, Gadella BM, De Rooij DG, Neefjes JJ. 2007. Multidrug resistance-associated protein 9 (ABCC12) is present in mouse and boar sperm. *Biochemical Journal* 406:31–40 DOI 10.1042/BJ20070292.

Osa-Andrews B, Tan KW, Sampson A, Iram SH. 2018. Development of novel intramolecular FRET-based ABC transporter biosensors to identify new substrates and modulators. *Pharmaceutics* 10:186 DOI 10.3390/pharmaceutics10040186.
Park H-A, Kubicki N, Gnyawali S, Chan YC, Roy S, Khanna S, Sen CK. 2011. Natural vitamin E α-tocotrienol protects against ischemic stroke by induction of multidrug resistance-associated protein 1. Stroke 42:2308–2314 DOI 10.1161/STROKEAHA.110.608547.

Payen LF, Gao M, Westlake CJ, Cole SP, Deeley RG. 2003. Role of carboxylate residues adjacent to the conserved core Walker B motifs in the catalytic cycle of multidrug resistance protein 1 (ABCC1). Journal of Biological Chemistry 278:38537–38547 DOI 10.1074/jbc.M305786200.

Perloff MD, Von Moltke LL, Marchand JE, Greenblatt DJ. 2001a. Ritonavir induces P-glycoprotein expression, multidrug resistance-associated protein (MRP1) expression, and drug transporter-mediated activity in a human intestinal cell line. Journal of Pharmaceutical Sciences 90:1829–1837 DOI 10.1002/jps.1133.

Perloff MD, Von Moltke LL, Marchand JE, Greenblatt DJ. 2001b. Ritonavir induces P-glycoprotein expression, multidrug resistance-associated protein (MRP1) expression, and drug transporter-mediated activity in a human intestinal cell line. Journal of Pharmaceutical Sciences 90:1829–1837 DOI 10.1002/jps.1133.

Peters G, Van Groeningen C. 1991. Clinical relevance of biochemical modulation of 5-fluorouracil. Annals of Oncology 2:469–480 DOI 10.1093/oxfordjournals.annonc.a057994.

Peterson BG, Tan KW, Osa-Andrews B, Iram SH. 2017. High-content screening of clinically tested anticancer drugs identifies novel inhibitors of human MRP1 (ABCC1). Pharmacological Research 119:313–326 DOI 10.1016/j.phrs.2017.02.024.

Pommier Y, Leo E, Zhang H, Marchand C. 2010. DNA topoisomerases and their poisoning by anticancer and antibacterial drugs. Chemistry & Biology 17:421–433 DOI 10.1016/j.chembiol.2010.04.012.

Poku VO. 2021. Identification and Characterization of Modulators of Human MRP1 (ABCC1) and Human MRP2 (ABCC2) Expression. South Dakota State University: ProQuest Dissertations & Theses Global.

Qadir M, O’Loughlin KL, Fricke SM, Williamson NA, Greco WR, Minderman H, Baer MR. 2005. Cyclosporin A is a broad-spectrum multidrug resistance modulator. Clinical Cancer Research 11:2320–2326 DOI 10.1158/1078-0432.CCR-04-1725.

Renes J, De Vries EG, Nienhuis EF, Jansen PL, Müller M. 1999. ATP-and glutathione-dependent transport of chemotherapeutic drugs by the multidrug resistance protein MRP1. British Journal of Pharmacology 126:681–688 DOI 10.1038/sj.bjp.0702360.

Roundhill E, Burchill S. 2013. Membrane expression of MRP-1, but not MRP-1 splicing or Pgp expression, predicts survival in patients with ESFT. British Journal of Cancer 109:195–206 DOI 10.1038/bjc.2013.168.

Sampson A, Peterson BG, Tan KW, Iram SH. 2019. Doxorubicin as a fluorescent reporter identifies novel MRP1 (ABCC1) inhibitors missed by calcein-based high content screening of anticancer agents. Biomedicine & Pharmacotherapy 118:109289 DOI 10.1016/j.biopha.2019.109289.

Sauna ZE, Peng X-H, Nandigama K, Tekle S, Ambudkar SV. 2004. The molecular basis of the action of disulfiram as a modulator of the multidrug resistance-linked ATP
binding cassette transporters MDR1 (ABCB1) and MRP1 (ABCC1). *Molecular Pharmacology* **65**:675–684 DOI 10.1124/mol.65.3.675.

**Schmitt S.** 2017. Intrinsic human multidrug transporters as helpers against Alzheimer’s Disease. Available at https://atlasofscience.org/intrinsic-human-multidrug-transporters-as-helpers-against-alzheimers-disease/ (accessed on 06 September 2020).

**Schmitt SM, Stefan K, Wiese M.** 2017. Pyrrolopyrimidine derivatives and purine analogs as novel activators of Multidrug Resistance-associated Protein 1 (MRP1, ABCC1). *Biochimica et Biophysica Acta (BBA)-Biomembranes* **1859**:69–79 DOI 10.1016/j.bbamem.2016.10.017.

**Schrenk D, Baus PR, Ermel N, Klein C, Vorderstemann B, Kauffmann HM.** 2001. Up-regulation of transporters of the MRP family by drugs and toxins. *Toxicology Letters* **120**:51–57 DOI 10.1016/s0378-4274(01)00306-x.

**Sekine T, Miyazaki H, Endou H.** 2006. Molecular physiology of renal organic anion transporters. *American Journal of Physiology-Renal Physiology* **290**:F251–F261 DOI 10.1152/ajprenal.00439.2004.

**Sharom FJ, Slot AJ, Molinski SV, Cole SP.** 2011. Mammalian multidrug-resistance proteins (MRPs). *Essays in Biochemistry* **50**:179–207 DOI 10.1042/bse0500179.

**Shitan N, Tanaka M, Terai K, Ueda K, Yazaki K.** 2007. Human MDR1 and MRP1 recognize berberine as their transport substrate. *Bioscience, Biotechnology, and Biochemistry* **71**:242–245 DOI 10.1271/bbb.60441.

**Shukla S, Ohnuma S, Ambudkar SV.** 2011. Improving cancer chemotherapy with modulators of ABC drug transporters. *Current Drug Targets* **12**:621–630 DOI 10.2174/138945011795378540.

**Si W, Shen J, Zheng H, Fan W.** 2019. The role and mechanisms of action of microRNAs in cancer drug resistance. *Clinical Epigenetics* **11**:1–24 DOI 10.1186/s13148-018-0606-9.

**Sivils JC, Gonzalez I, Bain LJ.** 2010. Mice lacking Mrp1 have reduced testicular steroid hormone levels and alterations in steroid biosynthetic enzymes. *General and Comparative Endocrinology* **167**:51–59 DOI 10.1016/j.ygcen.2010.02.019.

**Starling JJ, Shepard RL, Cao J, Law KL, Norman BH, Kroin JS, Ehhardt WJ, Baughman TM, Winter MA, Bell MG.** 1997. Pharmacological characterization of LY335979: a potent cyclopropyldibenzosuberane modulator of P-glycoprotein. *Advances in Enzyme Regulation* **37**:335–347 DOI 10.1016/S0065-2571(96)00021-0.

**Stride BD, Cole SP, Deeley RG.** 1999. Localization of a substrate specificity domain in the multidrug resistance protein. *Journal of Biological Chemistry* **274**:22877–22883 DOI 10.1074/jbc.274.32.22877.

**Sui L, Wang J, Li B-M.** 2008. Role of the phosphoinositide 3-kinase-Akt-mammalian target of the rapamycin signaling pathway in long-term potentiation and trace fear conditioning memory in rat medial prefrontal cortex. *Learning & Memory* **15**:762–776 DOI 10.1101/lm.1067808.

**Szakács G, Paterson JK, Ludwig JA, Booth-Genthe C, Gottesman MM.** 2006. Targeting multidrug resistance in cancer. *Nature Reviews Drug Discovery* **5**:219–234 DOI 10.1038/nrd1984.
Szakács G, Váradi A, Özvegy-Laczka C, Sarkadi B. 2008. The role of ABC transporters in drug absorption, distribution, metabolism, excretion and toxicity (ADME–Tox). *Drug discovery today* 13:379–393.

Takenaka S, Itoh T, Fujiwara R. 2013. Expression pattern of human ATP-binding cassette transporters in skin. *Pharmacology Research & Perspectives* 1.

Tan KW, Sampson A, Osa-Andrews B, Iram SH. 2018. Calcitriol and Calciptoril Modulate Transport Activity of ABC Transporters and Exhibit Selective Cytotoxicity in MRP1-overexpressing cells. *Drug Metabolism and Disposition: The Biological Fate of Chemicals* 46:1856–1866 DOI 10.1124/dmd.118.081612.

Tatebe S, Sinicrope FA, Kuo MT. 2002. Induction of multidrug resistance proteins MRP1 and MRP3 and gamma-glutamylcysteine synthetase gene expression by nonsteroidal anti-inflammatory drugs in human colon cancer cells. *Biochemical and Biophysical Research Communications* 290:1427–1433 DOI 10.1006/bbrc.2002.6367.

Tian J, Hu J, Liu G, Yin H, Chen M, Miao P, Bai P, Yin J. 2019. Altered Gene expression of ABC transporters, nuclear receptors and oxidative stress signaling in zebrafish embryos exposed to CdTe quantum dots. *Environmental Pollution* 244:588–599 DOI 10.1016/j.envpol.2018.10.092.

Tong X, Zhao J, Zhang Y, Mu P, Wang X. 2019. Expression levels of MRP1, GST-π, and GSK3β in ovarian cancer and the relationship with drug resistance and prognosis of patients. *Oncology Letters* 18:22–28.

Touhey S, O’Connor R, Plunkett S, Maguire A, Clynes M. 2002. Structure–activity relationship of indomethacin analogues for MRP-1, COX-1 and COX-2 inhibition: identification of novel chemotherapeutic drug resistance modulators. *European Journal of Cancer* 38:1661–1670 DOI 10.1016/S0959-8049(02)00128-4.

Toyoshima C. 2009. How Ca2+-ATPase pumps ions across the sarcoplasmic reticulum membrane. *Biochimica Et Biophysica Acta (BBA)-Molecular Cell Research* 1793:941–946 DOI 10.1016/j.bbamcr.2008.10.008.

Vankeerberghen A, Cuppens H, Cassiman J-J. 2002. The cystic fibrosis transmembrane conductance regulator: an intriguing protein with pleiotropic functions. *Journal of Cystic Fibrosis* 1:13–29 DOI 10.1016/S1569-1993(01)00003-0.

Vasiliou V, Vasiliou K, Nebert DW. 2009. Human ATP-binding cassette (ABC) transporter family. *Human Genomics* 3:1–10.

Verrier PJ, Bird D, B Burla B, Dassa E, Forestier C, Geisler M, Klein M, Kolukisaoglu Ü, Lee Y, Martinova E. 2008. Plant ABC proteins—a unified nomenclature and updated inventory. *Trends in Plant Science* 13:151–159 DOI 10.1016/j.tplants.2008.02.001.

Videira M, Reis RL, Brito MA. 2014. Deconstructing breast cancer cell biology and the mechanisms of multidrug resistance. *Biochimica Et Biophysica Acta (BBA)-Reviews on Cancer* 1846:312–325 DOI 10.1016/j.bbr.2014.07.011.

Visscher H, Ross CJ, Rassek S, Barhdadi A, Dubé M-P, Al-Saloos H, Sandor GS, Caron HN, van Dalen EC, Kremer LC. 2012. Pharmacogenomic prediction of anthracycline-induced cardiotoxicity in children. *Journal of Clinical Oncology* 30:1422–1428 DOI 10.1200/JCO.2010.34.3467.
Walsh N, Kennedy S, Larkin A-M, Tryfonopoulos D, Eustace AJ, Mahgoub T, Conway C, Oglesby I, Collins D, Ballot J. 2010. Membrane transport proteins in human melanoma: associations with tumour aggressiveness and metastasis. *British Journal of Cancer* 102:1157–1162 DOI 10.1038/sj.bjc.6605590.

Walsh N, Larkin A, Kennedy S, Connolly L, Ballot J, Ooi W, Gullo G, Crown J, Clynes M, O’Driscoll L. 2009. Expression of multidrug resistance markers ABCB1 (MDR-1/P-gp) and ABCC1 (MRP-1) in renal cell carcinoma. *BMC Urology* 9:1–7 DOI 10.1186/1471-2490-9-1.

Wessler JD, Grip LT, Mendell J, Giugliano RP. 2013. The P-glycoprotein transport system and cardiovascular drugs. *Journal of the American College of Cardiology* 61:2495–2502 DOI 10.1016/j.jacc.2013.02.058.

Wijnholds J, Evers R, van Leusden MR, Mol CA, Zaman GJ, Mayer U, Beijnen JH, Van Der Valk M, Krimp enfort P, Borst P. 1997. Increased sensitivity to anticancer drugs and decreased inflammatory response in mice lacking the multidrug resistance-associated protein. *Nature Medicine* 3:1275–1279 DOI 10.1038/nm1197-1275.

Wojnowski L, Kulle B, Schirmer M, Schlüter G, Schmidt A, Rosenberger A, Vonhof S, Bickeböll H, Toliat MR, Suk E-K. 2005. NAD (P) H oxidase and multidrug resistance protein genetic polymorphisms are associated with doxorubicin-induced cardiotoxicity. *Circulation* 112:3754–3762 DOI 10.1161/CIRCULATIONAHA.105.576850.

Yabuuchi H, S-i Takayanagi, Yoshinaga K, Taniguchi N, Aburatani H, Ishikawa T. 2002. ABCC13, an unusual truncated ABC transporter, is highly expressed in fetal human liver. *Biochemical and Biophysical Research Communications* 299:410–417 DOI 10.1016/S0006-291X(02)02658-X.

Yabuuchi H, Shimizu H, S-i Takayanagi, Ishikawa T. 2001. Multiple splicing variants of two new human ATP-binding cassette transporters, ABCC11 and ABCC12. *Biochemical and Biophysical Research Communications* 288:933–939 DOI 10.1006/bbrc.2001.5865.

Yang J, Song P, Zhou G. 2019. A study on the correlations of MRP-1 expression with the pathogenesis and prognosis of colorectal cancer. *Journal of the Balkan Union of Oncology* 24:84–90.

Yeung ML, Jeang KT. 2011. MicroRNAs and cancer therapeutics. *Pharmaceutical Research* 28:3043–3049 DOI 10.1007/s11095-011-0526-2.

Yin J, Deng X, Zhang J, Lin J. 2018. Current understanding of interactions between nanoparticles and ABC transporters in cancer cells. *Current Medicinal Chemistry* 25:5930–5944.

Ying L, Zu-an Z, Qing-hua L, Qing-yan K, Lei L, Tao C, Yong-ping W. 2014. RAD001 can reverse drug resistance of SGC7901/DDP cells. *Tumor Biology* 35:9171–9177 DOI 10.1007/s13277-014-1719-1.

Yuan T, Sun J, Tian J, Hu J, Yin H, Yin J. 2021. Involvement of ABC transporters in the detoxification of non-substrate nanoparticles in lung and cervical cancer cells. *Toxicology* 455:152762 DOI 10.1016/j.tox.2021.152762.
Zhang H, Patel A, Ma SL, Li XJ, Zhang YK, Yang PQ, Kathawala RJ, Wang YJ, Anreddy N, Fu LW, Chen ZS. 2014. In vitro, in vivo and ex vivo characterization of ibrutinib: a potent inhibitor of the efflux function of the transporter MRP1. *British Journal of Pharmacology* 171:5845–5857 DOI 10.1111/bph.12889.

Zhao X, Li Y, Du K, Wu Y, Liu L, Cui S, Zhang Y, Gao J, Keep RF, Xiang J. 2019. Involvement of human and canine MRP1 and MRP4 in benzylpenicillin transport. *PLOS ONE* 14:e0225702 DOI 10.1371/journal.pone.0225702.