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The Challenge of Exploiting ABCG2 in the Clinic

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Abstract

ABCG2, or breast cancer resistance protein (BCRP), is an ATP-binding cassette half transporter that has been shown to transport a wide range of substrates including chemotherapeutics, antivirals, antibiotics and flavonoids. Given its wide range of substrates, much work has been dedicated to developing ABCG2 as a clinical target. But where can we intervene clinically and how can we avoid the mistakes made in past clinical trials targeting P-glycoprotein? This review will summarize the normal tissue distribution, cancer tissue expression, substrates and inhibitors of ABCG2, and highlight the challenges presented in exploiting ABCG2 in the clinic. We discuss the possibility of inhibiting ABCG2, so as to increase oral bioavailability or increase drug penetration into sanctuary sites, especially the central nervous system; and at the other end of the spectrum, the possibility of improving ABCG2 function, in the case of gout caused by a single nucleotide polymphism. Together, these aspects of ABCG2/BCRP make the protein a target of continuing interest for oncologists, biologists, and pharmacologists.

Keywords

ABCG2/BCRP; Blood Brain Barrier; CNS Penetration; Drug Resistance; Gout; Oral Bioavailability; Q141K; Single nucleotide polymorphism

INTRODUCTION

The ABCG2 transporter was described nearly simultaneously by 3 different groups who gave it 3 different names. First, ABCG2 was termed BCRP, or breast cancer resistance protein, by Doug Ross's group who cloned the transporter from an MCF-7 breast cancer subline selected with doxorubicin in the presence of verapamil[1]. Shortly thereafter, the same gene was reported by Mike Dean's group, who discovered the transporter mining an expressed sequence tag database and named the protein ABCP since it was an ABC transporter highly expressed in the placenta[2]; and by our group, who named it MXR for mitoxantrone resistance protein, from a colon cancer subline selected in mitoxantrone[3].

Since the discovery of ABCG2, the number of reports characterizing substrates, inhibitors, polymorphisms and expression in normal and cancerous tissues has increased exponentially, much as was the case for P-glycoprotein (Pgp, MDR1, ABCB1) and the multidrug resistance associated protein (MRP1, ABCC1) after their discoveries. In this review, we will focus on the clinical challenges and opportunities ABCG2 presents with regard to cancer and cancer treatment.

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Gene Expression and Protein Structure

The *ABCG2* gene, located on chromosome 4, is over 66kb and contains 16 exons and 15 introns. In cell line models, high levels of *ABCG2* expression are often accompanied by rearrangements involving chromosome 4 or by gene amplification[4, 5]. The *ABCG2* promoter has been reported to contain estrogen[6], hypoxia[7] and progesterone response[8] elements that have been shown to control gene expression and a peroxisome proliferator-activated receptor γ (PPARγ) response element upstream of the ABCG2 gene has also been identified[9]. The promoter is methylated in selected cell lines; treatment with demethylating agents will increase expression. In other cell types, increased promoter acetylation following exposure to deacetylase inhibitors will increase gene expression[10]. Cytokines and growth factors[11],[12] as well as microRNAs[13, 14] have been shown to have variable effects on gene expression.

The ABCG2 protein is made up of 655 amino acids and runs as a 72 kDa protein in reducing conditions. It is has one N-terminal nucleotide binding domain (NBD) and 6 C-terminal transmembrane segments comprising one transmembrane domain (TMD); this is in a reverse configuration compared to other ABC transporters where the NBD is at the C-terminus and the TMD is at the N-terminus. ABCG2 is considered a half-transporter as most transporters have at least 2 NBDs and 2 TMDs. ABCG2 is found in the G family of transporters, which is made up of only half transporters. As a half transporter, ABCG2 must dimerize to form a functional transporter.

Substrates and Inhibitors of ABCG2

ABCG2, much like Pgp, has proven to be a promiscuous transporter in that multiple compounds of different chemical classes are numbered among its substrates. It is of course best known for its ability to transport chemotherapeutic agents, with mitoxantrone, topotecan and SN-38 (the active metabolite of irinotecan) being among the most studied substrates. However, ABCG2 has also been shown to confer resistance to organic anions, such as the glucuronide conjugate of SN-38[15]. In this regard, there is overlapping substrate specificity with both Pgp and the MRPs. Other substrates include flavopiridol[16]; camptothecins such as irinotecan (and its active metabolite SN-38)[17, 18], 9-aminocamptothecin[19] and diflomotecan[20]; indolocarbazoles including edotecarin[21] and becatecarin[22]; antifolates such as methotrexate and some of its polyglutamylated forms[23], GW1843 and raltitrexed[24] as well as others; photosensitizers such as 2-(1-hexyloxethyl)-2-devinylpyropheophorbide a (HPPH)[25], benzoporphyrin derivative monoacid ring A[25] and pyropheophorbide a methyl ester[26]; and kinase inhibitors such as gefitinib[27], imatinib[28], nilotinib[29] and JNJ-7706621[30]. A number of other substrates unrelated to cancer treatment have also been described including uric acid[31], HMG-CoA reductase inhibitors[32], antivirals[33], antibiotics[34, 35], carcinogens[36, 37] and dihydropyridines[38] as well as D-luciferin[39]. A selected list of substrates is provided in Table 1.

The search for ABCG2 inhibitors began with the discovery that fumitremorgin C (FTC) could reverse resistance in the mitoxantrone-selected S1-M1-3.2 cell line from which ABCG2 was cloned[40]. Some of the first ABCG2 inhibitors identified were also Pgp inhibitors, such as elacridar (GF120918)[41], biricodar (VX-710)[42], dofequidar (MS-209)[43] and tariquidar (XR-9576)[44]. Other inhibitors include dihydropyridines[45], tyrosine kinase inhibitors[46], flavonoids[47, 48], rotenoids[49] and botryllamides[50]. Other inhibitors of ABCG2 are provided in Table 2.

In the case of several molecularly targeted anticancer agents, it has been difficult to determine whether the drugs are substrates or inhibitors. Evidence for both types of interaction has been presented in several reports for imatinib, nilotinib, and

gefitinib[27–29, 51, 52]. It is clear that the drugs interact with ABCG2, and careful studies suggest a concentration dependence – a substrate at low concentrations and inhibitory properties at high concentrations. In patients, oral gefitinib has been shown to increase plasma levels of orally administered topotecan (discussed below), suggesting in vivo activity as an inhibitor.

Pharmacokinetic Effects of ABCG2 Single Nucleotide Polymorphisms

Several studies of single nucleotide polymorphisms (SNPs) in the *ABCG2* gene have been reported[53]. Among the over two dozen sequence variations reported for *ABCG2*, the C421A nucleotide change, resulting in a glutamine to lysine substitution in the translated protein, has received the most attention. This variant is found with high frequency in people of Chinese (35%) or Japanese (35%) descent, but less frequently in people of African-American (2–5%), Hispanic (10%), European (11–14%) or Middle Eastern (13%) descent[54]. The Q141K change has been shown to result in decreased plasma membrane expression, decreased or reduced ATPase activity compared to wild-type ABCG2[55–57]. The net effect is a reduction in transport of substrates. Whether this is primarily due to decreased plasma membrane expression or to impaired function of properly localized transporter has not been clearly delineated. *In vitro* models show varying degrees of impaired folding. Misfolding is detected by the endoplasmic reticulum associated degradation (ERAD) quality control system, resulting in ubiquitin-mediated proteasomal degradation[58]. The clinical impact of this SNP has been demonstrated, and linked to altered pharmacokinetics of topotecan[59], 9-aminocamptothecin[60], diflomotecan[61], sulfasalazine[62], and statins such as atorvastatin and rosuvastatin[63], as well as to increased incidence of gefitinib-related diarrhea[64]. Most striking, however, is the recent association of the Q141K SNPs in ABCG2 with gout, where impaired transport of uric acid leads to higher plasma concentrations and clinical manifestation of gout[31].

Clinically Important Normal Tissue Expression

Soon after the discovery of ABCG2, several studies were published aimed at identifying the normal tissue expression profile of ABCG2. The location and expression of ABCG2 in normal tissues lends clues to its likely role in normal physiology. A schematic representation is provided in Figure 1. Normal tissue localization suggests a role in determining drug distribution and normal tissue expression in the blood-brain barrier, blood-testis barrier, and maternal-fetal barrier[65]. Existence of these barriers has been confirmed in animal models lacking ABCG2. Other normal tissue roles, as suggested by expression in breast epithelium, have also been implicated[66]. Discussion of ABCG2 expression in normal tissues with potential for clinical intervention is provided below.

Gastrointestinal Tract

General studies examining expression of ABCG2 in normal human tissues revealed high levels of expression in the epithelium of the gut[67, 68]. When Taipalensuu and colleagues examined tissue samples from various sites along the gastrointestinal tract, higher expression of ABCG2 compared to ABCB1 was found in the jejunum[69]. *ABCG2* gene expression was found to decrease along the length of the gastrointestinal tract, with highest levels found in the duodenum and lowest levels found in the rectum[70]. Similarly, Hilgendorf et al also reported higher levels in the jejunum versus the colon[71].

Animal models have repeatedly demonstrated the significance of ABCG2 in limiting oral drug availability. Jonker and colleagues demonstrated in Abcb1a/b-deficient mice that the oral bioavailability of topotecan was 9-fold higher in mice when oral topotecan was coadministered with the ABCG2 inhibitor elacridar[72]. Similar results were reported by Allen

and colleagues who reported that coadministration of oral topotecan with the ABCG2 inhibitor Ko143 resulted in 4- to 6-fold higher plasma topotecan levels in Abcb1a/b-deficient mice compared to mice given oral topotecan alone[73]. Pretreatment of Abcb1a/b-deficient mice with elacridar increased the AUC of the investigational analgesic GV196771 16.4-fold compared to wild-type mice[74]. Studies in Abcg2-deficient mice reported higher plasma levels of orally administered compounds compared to wild-type mice including the aurora kinase inhibitor JNJ-7706621[30], erlotinib[75], sulfasalazine[76] and some dietary flavonoids[77]. Subsequent clinical trials in humans have demonstrated increased oral bioavailability of topotecan when it is coadministered with the ABCG2 inhibitors elacridar[78, 79] or gefitinib[80]. Thus, ABCG2 plays a major role in controlling the oral bioavailability of substrate compounds. Clinically, this means that some fraction of interpatient variation in drug exposure for ABCG2 substrate drugs is likely to be accounted for by differences in ABCG2 expression and function. The Q141K polymorphism is likely to result in increased drug exposure for orally administered anticancer compounds that are also substrates for ABCG2.

While the physiologic role of ABCG2 is not regulating intestinal uptake of topotecan and erlotinib, the transporter may serve a protective role by transporting dietary carcinogens. A few examples of the dietary carcinogens that are subject to transport by ABCG2 are given in Table 1. One hour after oral administration of PhIP, plasma levels of PhIP were 3.1-fold higher in *Abcg2*$^{-/-}$ mice compared to wild type mice, confirming the role of ABCG2 in limiting the uptake of the carcinogen[36]. Similarly, ABCG2 was shown to limit the intestinal absorption of the carcinogens 2-amino-3-methylimidazo[4,5-f]quinoline (IQ), 3-amino-1,4-dimethyl-5H-pyrido[4,3-b]indole (Trp-P-1) and aflatoxin B1 in a mouse model[37].

Blood-Brain Barrier

Given the high levels of ABC transporter expression in brain microvessels, groups began looking for ABCG2 expression at the blood brain barrier soon after its discovery. ABCG2 was localized to the luminal surface of the endothelial cells of the human brain, much as described for Pgp[68, 81], suggesting that ABCG2 forms part of the blood-brain barrier along with other transporters such ABCC1 and ABCC2[82]. Aronica et al found ABCG2 to be localized to the luminal surface of blood vessels in the human brain, but did not find ABCG2 in glial cells or neuronal cells[83]. In mice, Cisternino and colleagues reported that Abcg2 levels in brain microvessels were 700-fold higher than in the cortex. Interestingly, they also reported that Abcg2 expression was 3-fold higher in Abcb1-deficient mice, suggesting not only a compensatory role for Abcg2 in the brain, but also cooperativity between the two transporters.

These findings in tissue localization studies have been mirrored by functional studies in mouse models that show that not only is ABCG2 an important component of the blood-brain barrier, but more dramatically, there is marked cooperativity between Abcg2 and Abcb1 at the blood-brain barrier. In Abcg2-deficient mice, the brain penetration of imatinib 2 h after i.v. administration of imatinib (12.5 mg/kg) was 1.2-fold higher versus wild-type mice[84]. This was not observed in a similar study where brain imatinib levels were examined 1 h after imatinib administration, suggesting that differences in brain levels mediated by transporters are time-sensitive[85]. Area under the plasma and brain tissue concentration-time curve (AUC) levels of topotean in Abcb1a/b$^{-/-}$, Abcg2$^{-/-}$ mice were 12-fold higher than wild-type mice, compared to mice deficient in Abcb1a/b or Abcg2 alone, suggesting that both transporters must be inhibited to achieve a maximal effect[86]. Similar results were observed with lapatinib. While Polli et al found brain concentrations of lapatinib were similar in Abcg2$^{-/-}$ mice and only 3- to 4-fold higher in Abcb1a/b$^{-/-}$ mice compared to wild-type mice, brain levels were nearly 40-fold higher in Abcb1a/b$^{-/-}$, Abcg2$^{-/-}$ mice compared to wild-type mice after IV administration[87]. This was true at both high and low

concentrations of IV lapatinib. Lagas et al reported that brain accumulation of sorafenib was 4.3-fold higher in Abcg2$^{-/-}$ mice while it was 9.3-fold higher in Abcb1a/b$^{-/-}$, Abcg2$^{-/-}$ mice compared to wild-type; administration of sorafenib to wild-type with elacridar, a dual Pgp and Abcg2 inhibitor, resulted in brain accumulation levels similar to those seen in mice deficient in both Abcb1a/b and Abcg2[88]. This group also reported similar results for dasatinib[89], as did Chen et al[90]. Using gefitinib as a PET tracer, Kawamura and colleagues demonstrated 8-fold higher radioactivity in the brains of Abcb1a/b−/−, Abcg2−/− mice compared to wild-type[91]. Clinically, the expression of ABCG2 at the blood-brain barrier likely limits the access of anticancer agents that are substrates. For example, the tyrosine kinase inhibitors gefitinib, erlotinib and lapatinib developed for lung or breast cancer likely do not gain significant access to the CNS. Since both of these tumor types have predilection for CNS metastases, a very important new line of investigation will be to identify mechanisms to increase CNS entry, to evaluate safety, and then to study efficacy. Based on the animal work, however, inhibition of ABCG2 alone will not be sufficient, and inhibitors of multiple transporters will be needed. An immediate need is to determine how closely the data in the knock-out mouse studies reflects the physiology of the human blood brain barrier.

Renal Excretion

In our earlier studies examining ABCG2 expression in normal tissues, we localized ABCG2 to the cortical tubules of the kidney, and postulated a role for ABCG2 in the renal excretion of compounds[68]. Subsequent studies reported expression of ABCG2 at the brush border membrane of proximal tubules[92]. Mouse models confirmed the role of ABCG2 in the renal excretion of sulfate conjugates of E3040 and edaravone[93, 94].

One recently identified substrate points to an important physiologic role of ABCG2 in the kidney. Several genome-wide association studies have independently found SNPs in ABCG2 to be associated with higher uric acid levels and gout[95–97]. Studies in Xenopus oocytes injected with ABCG2 mRNA confirmed ABCG2 was a transporter of uric acid, as uric acid transport rates in oocytes injected with ABCG2 encoding the Q141K SNP were over 50% lower than rates in oocytes expressing wild-type ABCG2[31]. SNPs in ABCG2 are postulated to account for approximately 10% of gout cases in white males[31].

From an oncologic perspective, this observation raises the question of whether an increased incidence of tumor lysis syndrome might be observed in patients harboring the Q141K SNP. Indeed, it is striking to note the number of case reports in the literature of tumor lysis syndrome in the context of diseases or drugs not conventionally thought associated with this complication – sorafenib in hepatocellular carcinoma, imatinib in chronic myelogenous leukemia, flavopiridol in chronic lymphocytic leukemia[98–101]. Given that these compounds are all substrates of ABCG2, and inhibitors at higher concentrations, it is tempting to speculate that these isolated cases occur in patients with the Q141K SNP.

ABCG2 Expression in Cancer and Drug Resistance

Well over 10 years after the initial reports of the ABCG2 gene, its role in clinical drug resistance is still murky. The majority of data concerning the contribution of ABCG2 to drug resistance in cancer has been gathered for leukemia and table 3 summarizes results of studies measuring ABCG2 expression in leukemia. While most reports that examined ABCG2 expression in acute lymphoblastic leukemia (ALL) reported relatively low levels, higher levels seemed to be found in acute myelogenous leukemia (AML), but even here there are conflicting reports. In AML, early studies seemed to suggest a link between expression of ABCG2 and clinical outcome, but as many reports have suggested that no link exists (see Table 3). More recently, groups have been looking at the purported “stem cell”

population, and some studies have reported relatively high levels of expression of ABCG2 in stem cells or in the most primitive progenitor population[102–104]. The presence of a leukemic stem cell is well accepted, but the existence of a hierarchical model including stem cells in solid tumors is more controversial[105]. Some studies have identified stem cells based upon their ability to efflux Hoechst dye. These cells have increased levels of ABCG2 and are thus more drug resistant. However, selection of cells based upon a Hoechst dim phenotype is not sufficient for identification of the putative stem cell population because ABCG2 is also a differentiated phenotype expressed, as noted above, in multiple cell types. If a hierarchical model is confirmed for solid tumors, and a distinct long-lived cell population exists that contributes to repopulation of cancer after therapy, as the hypothesis suggests, then targeting ABCG2 or other protective mechanisms will be needed to eradicate this cell population.

One difficulty in determining the role of any ABC transporter in drug resistance is that studies often examine only one transporter, much as the case in mouse studies where examining mice lacking Abcg2 only showed modest increases in CNS uptake of some drugs[87]. When gene expression profiles were generated from 170 pretreatment blast samples obtained from patients with AML in a study by Wilson and colleagues, unsupervised clustering classified patients into 6 distinct groups. The group with the poorest disease free survival rates was found to have high expression of *ABCG2*, usually accompanied by *ABCB1* expression. This group also had the highest rate of resistant disease (77%). The fact that this group contained only 22 patients, only 13% of the total number of patients, suggests that these patients might be missed in studies that feature only a small cohort of patients, arguing for studies to feature larger numbers of patients and determine expression of multiple transporters.

Intriguing results from one study were recently reported by Jiang et al., who found higher ABCG2 and ABCB1 expression as well as lower OCT1 expression in lin-CD34+CD38- cells in CML samples[106]. As imatinib requires OCT1 to enter the cell, CML cells expressing lower levels of OCT1 would be expected to uptake lower levels of imatinib, and this would be compounded by expression of ABCB1 and ABCG2, both of which have been shown to transport imatinib. Thus, increased expression of ABCB1 and ABCG2 along with decreased expression of OCT1 might play a role in drug resistance in CML, protecting the CML stem cell and preventing imatinib from reaching its target.

In solid tumors, ABCG2 expression has been studied multiple times in only breast cancer and non-small cell lung cancer. Here again, conflicting results have been reported. In breast cancer, ABCG2 expression was reported to be generally low[107, 108] and only one study reported a correlation between ABCG2 expression and response[109]. Some studies in lung cancer do seem to suggest a correlation between ABCG2 expression and response[110–112]; however, all these studies involve platinum-based therapies. Since platinum compounds are not known to be transported by ABCG2, it is unclear exactly how ABCG2 expression could account for the resistance observed in ABCG2-positive tumors. More studies must be conducted before the role of ABCG2 in clinical drug resistance, if any, can be elucidated.

What is striking about some of the clinical studies is a lack of validated controls. Some clinical studies do not include any kind of validated cell line model as a frame of reference when referring to gene expression or protein levels as “high” or “low”. Or, only cell lines expressing extremely high levels of ABCG2 are used--levels which one would not expect to find in clinical samples. We have previously suggested the inclusion of cell lines expressing validated low but detectable expression of ABCG2, such as MCF-7 breast cancer cells, A549 lung cancer cells, HCC-2998 colon cancer cells or SF295 CNS cancer cells[65], and these cell lines were also found to have low but detectable levels of pheophorbide a

transport[113]. As shown in table 4, gene expression levels of *ABCG2* in drug-selected cell lines, even those selected with relatively low levels of drug, can have significantly higher *ABCG2* expression than unselected lines. If methods used in clinical studies cannot detect ABCG2 expression or function in cell lines known to express low but detectable levels of ABCG2, how can the conclusions of these studies be accepted?

Clinical Interventions with ABCG2

With its normal tissue expression profile and its potential role in clinical drug resistance, ABCG2 presents several points of possible clinical intervention. In cancer therapeutics, a strategy of ABCG2 inhibition could be employed to increase oral biovavailability of chemotherapy agents, increase brain penetration, or overcome cancer cell resistance. With regard to oral bioavailability, a limited number of clinical trials have already demonstrated the feasibility of coadministering dual ABCG2/Pgp inhibitors with oral chemotherapy[78–80]. Depending on the compounds being orally administered, inhibiting multiple ABC transporters would most likely be necessary. Coadministering an ABC transporter inhibitor with chemotherapeutic agents that are transporter substrates could theoretically decrease interpatient variability caused by transporter expression and increase ease of administration of oral agents. Additionally, dose-limiting diarrhea that is normally found when administering oral topotecan was not observed when topotecan was coadministered with elacridar[78]. However, it is not certain that the clinical benefits of IV therapies will be maintained when the drugs are administered orally, since peak levels and drug exposure can vary depending on route of administration. Thus, further clinical trials will be needed to quantify clinical benefit achieved by increasing oral bioavailability.

It should be noted that the impact of inhibiting ABCG2 in the intestine may also be limited by the fact that high local concentrations after oral administration of some substrates may be enough to overcome the transporter's effect. Several orally administered drugs including gefitinib, nilotinib, and imatinib have been shown to be substrates only at low concentrations and to behave as inhibitors at higher concentrations[27, 29]. Since concentrations in the gut would be expected to be relatively high, additional inhibition of transporters in the gut may not be necessary.

Concerns of high local substrate concentrations likely do not apply to the blood-brain barrier where very high endothelial ABCG2 levels have been observed. Further, it will probably be necessary to inhibit multiple ABC transporters at the blood-brain barrier to increase brain penetration. This has been repeatedly demonstrated in mouse models where the maximum brain penetration of tyrosine kinase inhibitors as well as topotecan was achieved in mice lacking the genes for both Abcg2 and Abcb1/2[86–89]. However, such proof in humans is lacking. While dual inhibitors of ABCG2 and Pgp such as elacridar, tariquidar and dofequidar are readily available and inhibit the blood-brain barrier in mice, what is lacking is a validated probe of ABCG2 (or Pgp) function in the human blood-brain barrier. Without such a probe to prove inhibition of transporters at the blood-brain barrier, results of clinical trials combining a tyrosine kinase inhibitor with an ABC transporter inhibitor would be difficult to interpret. However, several imaging agents have been studied that may be useful in this regard. N-desmethyl-loperamide is being explored for imaging Pgp in the CNS in patients[114] and animal studies suggest that radiolabeled gefitinib may be useful in this regard[91].

Clinical trials attempting to reverse ABCG2-mediated resistance would be an even more difficult undertaking, due partly to the fact that a role for ABCG2 in clinical resistance has not been clearly proven in any disease and also due to the lack of clinical success with Pgp inhibitors. If any clinical trials are attempted, they would probably be conducted with AML,

as the most data for ABCG2 expression seems to have been gathered with this disease, but, as mentioned above, conflicting data have been been reported. Indeed, we would argue that such trials should not be undertaken prior to the development of correlative assays to aid in the interpretation of clinical trial data. First, validated assays of ABCG2 and Pgp must be developed and routinely used to determine levels of expression of transporters. Additionally, functional imaging assays must be developed to prove that given inhibitors can alter drug accumulation in tumors and evaluate drug penetration into sanctuary sites such as the brain.

Clinical intervention for the Q141K SNP would require a completely opposite approach. If this SNP results in decreased transport of carcinogens in the gut and decreased urate transport in the kidneys, increasing expression or increasing transport efficiency of ABCG2 in these sites may provide increased protection from carcinogens or decreased incidence of gout. It has been shown that, for mutated forms of CFTR, a “pharmacologic chaperone” can be used to “rescue” the mutant protein and result in increased membrane expression[115, 116]. Our laboratory has shown that mitoxantrone can function as a pharmacologic chaperone for ABCG2, increasing levels, improving processing, and increasing cell surface expression[117–119]. The ideal pharmacologic chaperone for ABCG2 would be a compound that is able to increase protein expression or function while exhibiting no toxicity and which does not act as an inhibitor of the protein. Some studies have shown that some dietary flavoniods can increase protein expression along with gene expression of ABCG2 in the Caco-2 cell line model[120]; however, caution must be exercised as a number of flavonoids have also been shown to inhibit ABCG2.

In short, this is a very exciting time for studies of ABC transporters in general. Our understanding of the importance of the transporters in human physiology and disease has increased far beyond that original discovery of Pgp, with its sole role as a mediator of drug resistance in cancer. While the studies of the 1990’s failed to prove the Pgp hypothesis in drug resistance, we believe it would be unwise to assume that there will never be a role for ABC transporters as a target in cancer therapeutics.

References

1. Doyle LA, Yang W, Abruzzo LV, Krogmann T, Gao Y, Rishi AK, Ross DD. A multidrug resistance transporter from human MCF-7 breast cancer cells. Proc. Natl. Acad. Sci. U. S. A. 1998; 95(26): 15665–15670. [PubMed: 9861027]
2. Allikmets R, Schriml LM, Hutchinson A, Romano-Spica V, Dean M. A human placenta-specific ATP-binding cassette gene (ABCP) on chromosome 4q22 that is involved in multidrug resistance. Cancer Res. 1998; 58(23):5337–5339. [PubMed: 9850061]
3. Miyake K, Mickley L, Litman T, Zhan Z, Robey R, Cristensen B, Brangi M, Greenberger L, Dean M, Fojo T, Bates SE. Molecular cloning of cDNAs which are highly overexpressed in mitoxantrone-resistant cells: demonstration of homology to ABC transport genes. Cancer Res. 1999; 59(1):8–13. [PubMed: 9892175]
4. Knutsen T, Rao VK, Ried T, Mickley L, Schneider E, Miyake K, Ghadimi BM, Padilla-Nash H, Pack S, Greenberger L, Cowan K, Dean M, Fojo T, Bates S. Amplification of 4q21-q22 and the MXR gene in independently derived mitoxantrone-resistant cell lines. Genes Chromosomes Cancer. 2000; 27(1):110–116. [PubMed: 10564593]
5. Rao VK, Wangsa D, Robey RW, Huff L, Honjo Y, Hung J, Knutsen T, Ried T, Bates SE. Characterization of ABCG2 gene amplification manifesting as extrachromosomal DNA in mitoxantrone-selected SF295 human glioblastoma cells. Cancer Genet. Cytogenet. 2005; 160(2): 126–133. [PubMed: 15993268]
6. Ee PL, Kamalakaran S, Tonetti D, He X, Ross DD, Beck WT. Identification of a novel estrogen response element in the breast cancer resistance protein (ABCG2) gene. Cancer Res. 2004; 64(4): 1247–1251. [PubMed: 14973083]

7. Krishnamurthy P, Ross DD, Nakanishi T, Bailey-Dell K, Zhou S, Mercer KE, Sarkadi B, Sorrentino BP, Schuetz JD. The stem cell marker Bcrp/ABCG2 enhances hypoxic cell survival through interactions with heme. J. Biol. Chem. 2004; 279(23):24218–24225. [PubMed: 15044468]
8. Wang H, Lee EW, Zhou L, Leung PC, Ross DD, Unadkat JD, Mao Q. Progesterone receptor (PR) isoforms PRA and PRB differentially regulate expression of the breast cancer resistance protein in human placental choriocarcinoma BeWo cells. Mol. Pharmacol. 2008; 73(3):845–854. [PubMed: 18042733]
9. Szatmari I, Vamosi G, Brazda P, Balint BL, Benko S, Szeles L, Jeney V, Ozvegy-Laczka C, Szanto A, Barta E, Balla J, Sarkadi B, Nagy L. Peroxisome proliferator-activated receptor gamma-regulated ABCG2 expression confers cytoprotection to human dendritic cells. J Biol Chem. 2006; 281(33):23812–23823. [PubMed: 16785230]
10. To KK, Polgar O, Huff LM, Morisaki K, Bates SE. Histone modifications at the ABCG2 promoter following treatment with histone deacetylase inhibitor mirror those in multidrug-resistant cells. Mol. Cancer Res. 2008; 6(1):151–164. [PubMed: 18234970]
11. Yin L, Castagnino P, Assoian RK. ABCG2 expression and side population abundance regulated by a transforming growth factor beta-directed epithelial-mesenchymal transition. Cancer Res. 2008; 68(3):800–807. [PubMed: 18245481]
12. Evseenko DA, Paxton JW, Keelan JA. Independent regulation of apical and basolateral drug transporter expression and function in placental trophoblasts by cytokines, steroids, and growth factors. Drug Metab. Dispos. 2007; 35(4):595–601. [PubMed: 17237156]
13. To K, Robey R, Knutsen T, Zhan Z, Ried T, Bates S. Escape from hsa-miR-519c enables drug-resistant cells to maintain high expression of ABCG2. Mol. Cancer Ther. 2009; 8(10):2959–2968. [PubMed: 19825807]
14. Pan Y, Morris M, Yu A. MicroRNA-328 negatively regulates the expression of breast cancer resistance protein (BCRP/ABCG2) in human cancer cells. Mol. Pharmacol. 2009; 75(6):1374–1379. [PubMed: 19270061]
15. Nakatomi K, Yoshikawa M, Oka M, Ikegami Y, Hayasaka S, Sano K, Shiozawa K, Kawabata S, Soda H, Ishikawa T, Tanabe S, Kohno S. Transport of 7-ethyl-10-hydroxycamptothecin (SN-38) by breast cancer resistance protein ABCG2 in human lung cancer cells. Biochem. Biophys. Res. Commun. 2001; 288(4):827–832. [PubMed: 11688982]
16. Robey RW, Medina-Perez WY, Nishiyama K, Lahusen T, Miyake K, Litman T, Senderowicz AM, Ross DD, Bates SE. Overexpression of the ATP-binding cassette half-transporter, ABCG2 (MXR/BCRP/ABCP1), in flavopiridol-resistant human breast cancer cells. Clin. Cancer Res. 2001; 7(1):145–152. [PubMed: 11205902]
17. Kawabata S, Oka M, Shiozawa K, Tsukamoto K, Nakatomi K, Soda H, Fukuda M, Ikegami Y, Sugahara K, Yamada Y, Kamihira S, Doyle LA, Ross DD, Kohno S. Breast cancer resistance protein directly confers SN-38 resistance of lung cancer cells. Biochem. Biophys. Res. Commun. 2001; 280(5):1216–1223. [PubMed: 11162657]
18. Ishii M, Iwahana M, Mitsui I, Minami M, Imagawa S, Tohgo A, Ejima A. Growth inhibitory effect of a new camptothecin analog, DX-8951f, on various drug-resistant sublines including BCRP-mediated camptothecin derivative-resistant variants derived from the human lung cancer cell line PC-6. Anticancer Drugs. 2000; 11(5):353–362. [PubMed: 10912951]
19. Rajendra R, Gounder MK, Saleem A, Schellens JH, Ross DD, Bates SE, Sinko P, Rubin EH. Differential effects of the breast cancer resistance protein on the cellular accumulation and cytotoxicity of 9-aminocamptothecin and 9-nitrocamptothecin. Cancer Res. 2003; 63(12):3228–3233. [PubMed: 12810652]
20. Bates SE, Medina-Perez WY, Kohlhagen G, Antony S, Nadjem T, Robey RW, Pommier Y. ABCG2 mediates differential resistance to SN-38 and homocamptothecins. J. Pharmacol. Exp. Ther. 2004; 310:836–842. [PubMed: 15075385]
21. Komatani H, Kotani H, Hara Y, Nakagawa R, Matsumoto M, Arakawa H, Nishimura S. Identification of breast cancer resistant protein/mitoxantrone resistance/placenta-specific, ATP-binding cassette transporter as a transporter of NB-506 and J-107088, topoisomerase I inhibitors with an indolocarbazole structure. Cancer Res. 2001; 61(7):2827–2832. [PubMed: 11306452]
22. Robey R, Obrzut T, Shukla S, Polgar O, Macalou S, Bahr J, Di Pietro A, Ambudkar S, Bates S. Becatecarin (rebeccamycin analog, NSC 655649) is a transport substrate and induces expression of

the ATP-binding cassette transporter, ABCG2, in lung carcinoma cells. Cancer Chemother. Pharmacol. 2009; 64(3):575–583. [PubMed: 19132374]

23. Chen ZS, Robey RW, Belinsky MG, Shchaveleva I, Ren XQ, Sugimoto Y, Ross DD, Bates SE, Kruh GD. Transport of methotrexate, methotrexate polyglutamates, and 17beta-estradiol 17-(beta-D-glucuronide) by ABCG2: effects of acquired mutations at R482 on methotrexate transport. Cancer Res. 2003; 63(14):4048–4054. [PubMed: 12874005]
24. Shafran A, Ifergan I, Bram E, Jansen G, Kathmann I, Peters GJ, Robey RW, Bates SE, Assaraf YG. ABCG2 harboring the Gly482 mutation confers high-level resistance to various hydrophilic antifolates. Cancer Res. 2005; 65(18):8414–8422. [PubMed: 16166320]
25. Liu W, Baer MR, Bowman MJ, Pera P, Zheng X, Morgan J, Pandey RA, Oseroff AR. The tyrosine kinase inhibitor imatinib mesylate enhances the efficacy of photodynamic therapy by inhibiting ABCG2. Clin. Cancer Res. 2007; 13(8):2463–2470. [PubMed: 17438106]
26. Robey RW, Steadman K, Polgar O, Bates SE. ABCG2-mediated transport of photosensitizers: potential impact on photodynamic therapy. Cancer Biol. Ther. 2005; 4(2):187–194. [PubMed: 15684613]
27. Elkind NB, Szentpetery Z, Apati A, Ozvegy-Laczka C, Varady G, Ujhelly O, Szabo K, Homolya L, Varadi A, Buday L, Keri G, Nemet K, Sarkadi B. Multidrug transporter ABCG2 prevents tumor cell death induced by the epidermal growth factor receptor inhibitor Iressa (ZD1839, Gefitinib). Cancer Res. 2005; 65(5):1770–1777. [PubMed: 15753373]
28. Burger H, van Tol H, Boersma AW, Brok M, Wiemer EA, Stoter G, Nooter K. Imatinib mesylate (STI571) is a substrate for the breast cancer resistance protein (BCRP)/ABCG2 drug pump. Blood. 2004; 104(9):2940–2942. [PubMed: 15251980]
29. Brendel C, Scharenberg C, Dohse M, Robey RW, Bates SE, Shukla S, Ambudkar SV, Wang Y, Wennemuth G, Burchert A, Boudriot U, Neubauer A. Imatinib mesylate and nilotinib (AMN107) exhibit high-affinity interaction with ABCG2 on primitive hematopoietic stem cells. Leukemia. 2007; 21(6):1267–1275. [PubMed: 17519960]
30. Seamon JA, Rugg CA, Emanuel S, Calcagno AM, Ambudkar SV, Middleton SA, Butler J, Borowski V, Greenberger LM. Role of the ABCG2 drug transporter in the resistance and oral bioavailability of a potent cyclin-dependent kinase/Aurora kinase inhibitor. Mol. Cancer Ther. 2006; 5(10):2459–2467. [PubMed: 17041089]
31. Woodward O, Köttgen A, Coresh J, Boerwinkle E, Guggino W, Köttgen M. Identification of a urate transporter, ABCG2, with a common functional polymorphism causing gout. Proc. Natl. Acad. Sci. U. S. A. 2009; 106(25):10338–10342. [PubMed: 19506252]
32. Huang L, Wang Y, Grimm S. ATP-dependent transport of rosuvastatin in membrane vesicles expressing breast cancer resistance protein. Drug Metab. Dispos. 2006; 34(5):738–742. [PubMed: 16415124]
33. Wang X, Nitanda T, Shi M, Okamoto M, Furukawa T, Sugimoto Y, Akiyama S, Baba M. Induction of cellular resistance to nucleoside reverse transcriptase inhibitors by the wild-type breast cancer resistance protein. Biochem. Pharmacol. 2004; 68(7):1363–1370. [PubMed: 15345326]
34. Ando T, Kusuhara H, Merino G, Alvarez AI, Schinkel AH, Sugiyama Y. Involvement of breast cancer resistance protein (ABCG2) in the biliary excretion mechanism of fluoroquinolones. Drug Metab. Dispos. 2007; 35(10):1873–1879. [PubMed: 17639028]
35. Merino G, Alvarez A, Pulido M, Molina A, Schinkel A, Prieto J. Breast cancer resistance protein (BCRP/ABCG2) transports fluoroquinolone antibiotics and affects their oral availability, pharmacokinetics, and milk secretion. Drug Metab. Dispos. 2006; 34(4):690–695. [PubMed: 16434544]
36. van Herwaarden AE, Jonker JW, Wagenaar E, Brinkhuis RF, Schellens JH, Beijnen JH, Schinkel AH. The breast cancer resistance protein (Bcrp1/Abcg2) restricts exposure to the dietary carcinogen 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine. Cancer Res. 2003; 63(19):6447–6452. [PubMed: 14559835]
37. van Herwaarden AE, Wagenaar E, Karnekamp B, Merino G, Jonker JW, Schinkel AH. Breast cancer resistance protein (Bcrp1/Abcg2) reduces systemic exposure of the dietary carcinogens aflatoxin B1, IQ and Trp-P-1 but also mediates their secretion into breast milk. Carcinogenesis. 2006; 27(1):123–130. [PubMed: 16000399]

38. Shukla S, Robey RW, Bates SE, Ambudkar SV. The calcium channel blockers, 1,4-dihydropyridines, are substrates of the multidrug resistance-linked ABC drug transporter, ABCG2. Biochemistry. 2006; 45(29):8940–8951. [PubMed: 16846237]
39. Zhang Y, Byun Y, Ren Y, Liu J, Laterra J, Pomper M. Identification of inhibitors of ABCG2 by a bioluminescence imaging-based high-throughput assay. Cancer Res. 2009; 69(14):5867–5875. [PubMed: 19567678]
40. Rabindran SK, He H, Singh M, Brown E, Collins KI, Annable T, Greenberger LM. Reversal of a novel multidrug resistance mechanism in human colon carcinoma cells by fumitremorgin C. Cancer Res. 1998; 58(24):5850–5858. [PubMed: 9865745]
41. de Bruin M, Miyake K, Litman T, Robey R, Bates SE. Reversal of resistance by GF120918 in cell lines expressing the ABC half-transporter, MXR. Cancer Lett. 1999; 146(2):117–126. [PubMed: 10656616]
42. Minderman H, O'Loughlin KL, Pendyala L, Baer MR. VX-710 (biricodar) increases drug retention and enhances chemosensitivity in resistant cells overexpressing P-glycoprotein, multidrug resistance protein, and breast cancer resistance protein. Clin Cancer Res. 2004; 10(5):1826–1834. [PubMed: 15014037]
43. Katayama R, Koike S, Sato S, Sugimoto Y, Tsuruo T, Fujita N. Dofequidar fumarate sensitizes cancer stem-like side population cells to chemotherapeutic drugs by inhibiting ABCG2/BCRP-mediated drug export. Cancer Sci. 2009; 100(11):2060–2068. [PubMed: 19673889]
44. Robey RW, Steadman K, Polgar O, Morisaki K, Blayney M, Mistry P, Bates SE. Pheophorbide a is a specific probe for ABCG2 function and inhibition. Cancer Res. 2004; 64(4):1242–1246. [PubMed: 14973080]
45. Zhou XF, Yang X, Wang Q, Coburn RA, Morris ME. Effects of dihydropyridines and pyridines on multidrug resistance mediated by breast cancer resistance protein: in vitro and in vivo studies. Drug Metab. Dispos. 2005; 33(8):1220–1228. [PubMed: 15908473]
46. Ozvegy-Laczka C, Hegedus T, Varady G, Ujhelly O, Schuetz JD, Varadi A, Keri G, Orfi L, Nemet K, Sarkadi B. High-affinity interaction of tyrosine kinase inhibitors with the ABCG2 multidrug transporter. Mol. Pharmacol. 2004; 65(6):1485–1495. [PubMed: 15155841]
47. Zhang S, Yang X, Morris ME. Flavonoids are inhibitors of breast cancer resistance protein (ABCG2)-mediated transport. Mol. Pharmacol. 2004; 65(5):1208–1216. [PubMed: 15102949]
48. Ahmed-Belkacem A, Pozza A, Munoz-Martinez F, Bates SE, Castanys S, Gamarro F, Di Pietro A, Perez-Victoria JM. Flavonoid structure-activity studies identify 6-prenylchrysin and tectochrysin as potent and specific inhibitors of breast cancer resistance protein ABCG2. Cancer Res. 2005; 65(11):4852–4860. [PubMed: 15930306]
49. Ahmed-Belkacem A, Macalou S, Borrelli F, Capasso R, Fattorusso E, Taglialatela-Scafati O, Di Pietro A. Nonprenylated rotenoids, a new class of potent breast cancer resistance protein inhibitors. J. Med. Chem. 2007; 50(8):1933–1938. [PubMed: 17341062]
50. Henrich C, Robey R, Takada K, Bokesch H, Bates S, Shukla S, Ambudkar S, McMahon J, Gustafson K. Botryllamides: natural product inhibitors of ABCG2. ACS Chem. Biol. 2009; 4(8): 637–647. [PubMed: 19555120]
51. Stewart CF, Leggas M, Schuetz JD, Panetta JC, Cheshire PJ, Peterson J, Daw N, Jenkins JJ, 3rd; Gilbertson R, Germain GS, Harwood FC, Houghton PJ. Gefitinib enhances the antitumor activity and oral bioavailability of irinotecan in mice. Cancer Res. 2004; 64(20):7491–7499. [PubMed: 15492275]
52. Tiwari A, Sodani K, Wang S, Kuang Y, Ashby CJ, Chen X, Chen Z. Nilotinib (AMN107, Tasigna) reverses multidrug resistance by inhibiting the activity of the ABCB1/Pgp and ABCG2/BCRP/MXR transporters. Biochem. Pharmacol. 2009; 78(2):153–161. [PubMed: 19427995]
53. Noguchi K, Katayama K, Mitsuhashi J, Sugimoto Y. Functions of the breast cancer resistance protein (BCRP/ABCG2) in chemotherapy. Adv. Drug Deliv. Rev. 2009; 61(1):26–33. [PubMed: 19111841]
54. Lepper ER, Nooter K, Verweij J, Acharya MR, Figg WD, Sparreboom A. Mechanisms of resistance to anticancer drugs: the role of the polymorphic ABC transporters ABCB1 and ABCG2. Pharmacogenomics. 2005; 6(2):115–138. [PubMed: 15882131]

55. Imai Y, Nakane M, Kage K, Tsukahara S, Ishikawa E, Tsuruo T, Miki Y, Sugimoto Y. 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. 2002; 1(8):611–616. [PubMed: 12479221]
56. Mizuarai S, Aozasa N, Kotani H. Single nucleotide polymorphisms result in impaired membrane localization and reduced atpase activity in multidrug transporter ABCG2. Int. J. Cancer. 2004; 109(2):238–246. [PubMed: 14750175]
57. Morisaki K, Robey RW, Ozvegy-Laczka C, Honjo Y, Polgar O, Steadman K, Sarkadi B, Bates SE. Single nucleotide polymorphisms modify the transporter activity of ABCG2. Cancer Chemother. Pharmacol. 2005; 56(2):161–172. [PubMed: 15838659]
58. Furukawa T, Wakabayashi K, Tamura A, Nakagawa H, Morishima Y, Osawa Y, Ishikawa T. Major SNP (Q141K) variant of human ABC transporter ABCG2 undergoes lysosomal and proteasomal degradations. Pharm. Res. 2009; 26(2):469–479. [PubMed: 18958403]
59. Sparreboom A, Loos WJ, Burger H, Sissung TM, Verweij J, Figg WD, Nooter K, Gelderblom H. Effect of ABCG2 Genotype on the Oral Bioavailability of Topotecan. Cancer Biol. Ther. 2005; 4(6):650–658. [PubMed: 15908806]
60. Zamboni WC, Ramanathan RK, McLeod HL, Mani S, Potter DM, Strychor S, Maruca LJ, King CR, Jung LL, Parise RA, Egorin MJ, Davis TA, Marsh S. Disposition of 9-nitrocamptothecin and its 9-aminocamptothecin metabolite in relation to ABC transporter genotypes. Invest. New Drugs. 2006; 24(5):393–401. [PubMed: 16505951]
61. Sparreboom A, Gelderblom H, Marsh S, Ahluwalia R, Obach R, Principe P, Twelves C, Verweij J, McLeod HL. Diflomotecan pharmacokinetics in relation to ABCG2 421C>A genotype. Clin. Pharmacol. Ther. 2004; 76(1):38–44. [PubMed: 15229462]
62. Urquhart B, Ware J, Tirona R, Ho R, Leake B, Schwarz U, Zaher H, Palandra J, Gregor J, Dresser G, Kim R. Breast cancer resistance protein (ABCG2) and drug disposition: intestinal expression, polymorphisms and sulfasalazine as an in vivo probe. Pharmacogenet. Genomics. 2008; 18(5): 439–448. [PubMed: 18408567]
63. Keskitalo J, Zolk O, Fromm M, Kurkinen K, Neuvonen P, Niemi M. ABCG2 polymorphism markedly affects the pharmacokinetics of atorvastatin and rosuvastatin. Clin. Pharmacol. Ther. 2009; 86(2):197–203. [PubMed: 19474787]
64. Cusatis G, Gregorc V, Li J, Spreafico A, Ingersoll RG, Verweij J, Ludovini V, Villa E, Hidalgo M, Sparreboom A, Baker SD. Pharmacogenetics of ABCG2 and adverse reactions to gefitinib. J. Natl. Cancer Inst. 2006; 98(23):1739–1742. [PubMed: 17148776]
65. Robey RW, Polgar O, Deeken J, To KW, Bates SE. ABCG2: determining its relevance in clinical drug resistance. Cancer Metastasis Rev. 2007; 26(1):39–57. [PubMed: 17323127]
66. Jonker JW, Merino G, Musters S, van Herwaarden AE, Bolscher E, Wagenaar E, Mesman E, Dale TC, Schinkel AH. The breast cancer resistance protein BCRP (ABCG2) concentrates drugs and carcinogenic xenotoxins into milk. Nat. Med. 2005; 11(2):127–129. [PubMed: 15685169]
67. Maliepaard M, Scheffer GL, Faneyte IF, van Gastelen MA, Pijnenborg AC, Schinkel AH, van De Vijver MJ, Scheper RJ, Schellens JH. Subcellular localization and distribution of the breast cancer resistance protein transporter in normal human tissues. Cancer Res. 2001; 61(8):3458–3464. [PubMed: 11309308]
68. Fetsch P, Abati A, Litman T, Morisaki K, Honjo Y, Mittal K, Bates S. Localization of the ABCG2 mitoxantrone resistance-associated protein in normal tissues. Cancer Lett. 2006; 235(1):84–92. [PubMed: 15990223]
69. Taipalensuu J, Tornblom H, Lindberg G, Einarsson C, Sjoqvist F, Melhus H, Garberg P, Sjostrom B, Lundgren B, Artursson P. Correlation of gene expression of ten drug efflux proteins of the ATP-binding cassette transporter family in normal human jejunum and in human intestinal epithelial Caco-2 cell monolayers. J. Pharmacol. Exp. Ther. 2001; 299(1):164–170. [PubMed: 11561076]
70. Gutmann H, Hruz P, Zimmermann C, Beglinger C, Drewe J. Distribution of breast cancer resistance protein (BCRP/ABCG2) mRNA expression along the human GI tract. Biochem. Pharmacol. 2005; 70(5):695–699. [PubMed: 15998509]

71. Hilgendorf C, Ahlin G, Seithel A, Artursson P, Ungell A, Karlsson J. Expression of thirty-six drug transporter genes in human intestine, liver, kidney, and organotypic cell lines. Drug Metab. Dispos. 2007; 35(8):1333–1340. [PubMed: 17496207]
72. Jonker JW, Smit JW, Brinkhuis RF, Maliepaard M, Beijnen JH, Schellens JH, Schinkel AH. Role of breast cancer resistance protein in the bioavailability and fetal penetration of topotecan. J. Natl. Cancer Inst. 2000; 92(20):1651–1656. [PubMed: 11036110]
73. Allen JD, van Loevezijn A, Lakhai JM, van der Valk M, van Tellingen O, Reid G, Schellens JHM, Koomen GJ, Schinkel AH. Potent and Specific Inhibition of the Breast Cancer Resistance Protein Multidrug Transporter in Vitro and in Mouse Intestine by a Novel Analogue of Fumitremorgin C. Mol. Cancer Ther. 2002; 1(6):417–425. [PubMed: 12477054]
74. Polli JW, Baughman TM, Humphreys JE, Jordan KH, Mote AL, Webster LO, Barnaby RJ, Vitulli G, Bertolotti L, Read KD, Serabjit-Singh CJ. The systemic exposure of an N-methyl-D-aspartate receptor antagonist is limited in mice by the P-glycoprotein and breast cancer resistance protein efflux transporters. Drug Metab. Dispos. 2004; 32(7):722–726. [PubMed: 15205387]
75. Marchetti S, de Vries NA, Buckle T, Bolijn MJ, van Eijndhoven MA, Beijnen JH, Mazzanti R, van Tellingen O, Schellens JH. Effect of the ATP-binding cassette drug transporters ABCB1, ABCG2, and ABCC2 on erlotinib hydrochloride (Tarceva) disposition in in vitro and in vivo pharmacokinetic studies employing Bcrp1−/−/Mdr1a/1b−/− (triple-knockout) and wild-type mice. Mol. Cancer Ther. 2008; 7(8):2280–2287. [PubMed: 18723475]
76. Zaher H, Khan AA, Palandra J, Brayman TG, Yu L, Ware JA. Breast cancer resistance protein (Bcrp/abcg2) is a major determinant of sulfasalazine absorption and elimination in the mouse. Mol. Pharm. 2006; 3(1):55–61. [PubMed: 16686369]
77. Enokizono J, Kusuhara H, Sugiyama Y. Effect of breast cancer resistance protein (Bcrp/Abcg2) on the disposition of phytoestrogens. Mol. Pharmacol. 2007; 72(4):967–975. [PubMed: 17644650]
78. Kuppens IE, Witteveen EO, Jewell RC, Radema SA, Paul EM, Mangum SG, Beijnen JH, Voest EE, Schellens JH. A phase I, randomized, open-label, parallel-cohort, dose-finding study of elacridar (GF120918) and oral topotecan in cancer patients. Clin. Cancer Res. 2007; 13(11):3276–3285. [PubMed: 17545533]
79. Kruijtzer CM, Beijnen JH, Rosing H, Ten Bokkel Huinink WW, Schot M, Jewell RC, Paul EM, Schellens JH. Increased Oral Bioavailability of Topotecan in Combination With the Breast Cancer Resistance Protein and P-Glycoprotein Inhibitor GF120918. J. Clin. Oncol. 2002; 20(13):2943–2950. [PubMed: 12089223]
80. Furman W, Navid F, Daw N, McCarville M, McGregor L, Spunt S, Rodriguez-Galindo C, Panetta J, Crews K, Wu J, Gajjar A, Houghton P, Santana V, Stewart C. Tyrosine kinase inhibitor enhances the bioavailability of oral irinotecan in pediatric patients with refractory solid tumors. J. Clin. Oncol. 2009; 27(27):4599–4604. [PubMed: 19687340]
81. Cooray HC, Blackmore CG, Maskell L, Barrand MA. Localisation of breast cancer resistance protein in microvessel endothelium of human brain. Neuroreport. 2002; 13(16):2059–2063. [PubMed: 12438926]
82. Deeken JF, Loscher W. The blood-brain barrier and cancer: transporters, treatment, and Trojan horses. Clin. Cancer Res. 2007; 13(6):1663–1674. [PubMed: 17363519]
83. Aronica E, Gorter J, Redeker S, van Vliet E, Ramkema M, Scheffer G, Scheper R, van der Valk P, Leenstra S, Baayen J, Spliet W, Troost D. Localization of breast cancer resistance protein (BCRP) in microvessel endothelium of human control and epileptic brain. Epilepsia. 2005; 46(6):849–857. [PubMed: 15946326]
84. Breedveld P, Pluim D, Cipriani G, Wielinga P, van Tellingen O, Schinkel AH, Schellens JH. The effect of Bcrp1 (Abcg2) on the in vivo pharmacokinetics and brain penetration of imatinib mesylate (Gleevec): implications for the use of breast cancer resistance protein and P-glycoprotein inhibitors to enable the brain penetration of imatinib in patients. Cancer Res. 2005; 65(7):2577–2582. [PubMed: 15805252]
85. Bihorel S, Camenisch G, Lemaire M, Scherrmann JM. Influence of breast cancer resistance protein (Abcg2) and p-glycoprotein (Abcb1a) on the transport of imatinib mesylate (Gleevec) across the mouse blood-brain barrier. J. Neurochem. 2007; 102(6):1749–1757. [PubMed: 17696988]

86. de Vries NA, Zhao J, Kroon E, Buckle T, Beijnen JH, van Tellingen O. P-glycoprotein and breast cancer resistance protein: two dominant transporters working together in limiting the brain penetration of topotecan. Clin. Cancer Res. 2007; 13(21):6440–6449. [PubMed: 17975156]

87. Polli J, Olson K, Chism J, John-Williams L, Yeager R, Woodard S, Otto V, Castellino S, Demby V. An unexpected synergist role of P-glycoprotein and breast cancer resistance protein on the central nervous system penetration of the tyrosine kinase inhibitor lapatinib (N-{3-chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methylsulfonyl)ethyl]amino}methyl)-2-furyl]-4-quinazolinamine; GW572016). Drug. Metab. Dispos. 2009; 37(2):439–442. [PubMed: 19056914]

88. Lagas J, van Waterschoot R, Sparidans R, Wagenaar E, Beijnen J, Schinkel A. Breast cancer resistance protein and P-glycoprotein limit sorafenib brain accumulation. Mol. Cancer Ther. 2010; 9(2):319–326. [PubMed: 20103600]

89. Lagas J, van Waterschoot R, van Tilburg V, Hillebrand M, Lankheet N, Rosing H, Beijnen J, Schinkel A. Brain accumulation of dasatinib is restricted by P-glycoprotein (ABCB1) and breast cancer resistance protein (ABCG2) and can be enhanced by elacridar treatment. Clin. Cancer Res. 2009; 15(7):2344–2351. [PubMed: 19276246]

90. Chen Y, Agarwal S, Shaik N, Chen C, Yang Z, Elmquist W. P-glycoprotein and breast cancer resistance protein influence brain distribution of dasatinib. J. Pharmacol. Exp. Ther. 2009; 330(3): 956–963. [PubMed: 19491323]

91. Kawamura K, Yamasaki T, Yui J, Hatori A, Konno F, Kumata K, Irie T, Fukumura T, Suzuki K, Kanno I, Zhang M. In vivo evaluation of P-glycoprotein and breast cancer resistance protein modulation in the brain using [(11)C]gefitinib. Nucl. Med. Biol. 2009; 36(3):239–246. [PubMed: 19324269]

92. Huls M, Brown CD, Windass AS, Sayer R, van den Heuvel JJ, Heemskerk S, Russel FG, Masereeuw R. The breast cancer resistance protein transporter ABCG2 is expressed in the human kidney proximal tubule apical membrane. Kidney Int. 2008; 73(2):220–225. [PubMed: 17978814]

93. Mizuno N, Suzuki M, Kusuhara H, Suzuki H, Takeuchi K, Niwa T, Jonker JW, Sugiyama Y. Impaired renal excretion of 6-hydroxy-5,7-dimethyl-2-methylamino-4-(3-pyridylmethyl) benzothiazole (E3040) sulfate in breast cancer resistance protein (BCRP1/ABCG2) knockout mice. Drug Metab. Dispos. 2004; 32(9):898–901. [PubMed: 15319327]

94. Mizuno N, Takahashi T, Kusuhara H, Schuetz JD, Niwa T, Sugiyama Y. Evaluation of the role of breast cancer resistance protein (BCRP/ABCG2) and multidrug resistance-associated protein 4 (MRP4/ABCC4) in the urinary excretion of sulfate and glucuronide metabolites of edaravone (MCI-186; 3-methyl-1-phenyl-2-pyrazolin-5-one). Drug Metab. Dispos. 2007; 35(11):2045–2052. [PubMed: 17682070]

95. Dehghan A, Köttgen A, Yang Q, Hwang S, Kao W, Rivadeneira F, Boerwinkle E, Levy D, Hofman A, Astor B, Benjamin E, van Duijn C, Witteman J, Coresh J, Fox C. Association of three genetic loci with uric acid concentration and risk of gout: a genome-wide association study. Lancet. 2008; 372(9654):1953–1961. [PubMed: 18834626]

96. Kolz M, Johnson T, Sanna S, Teumer A, Vitart V, Perola M, Mangino M, Albrecht E, Wallace C, Farrall M, Johansson A, Nyholt D, Aulchenko Y, Beckmann J, Bergmann S, Bochud M, Brown M, Campbell H, Connell J, Dominiczak A, Homuth G, Lamina C, McCarthy M, Meitinger T, Mooser V, Munroe P, Nauck M, Peden J, Prokisch H, Salo P, Salomaa V, Samani N, Schlessinger D, Uda M, Völker U, Waeber G, Waterworth D, Wang-Sattler R, Wright A, Adamski J, Whitfield J, Gyllensten U, Wilson J, Rudan I, Pramstaller P, Watkins H, Doering A, Wichmann H, Spector T, Peltonen L, Völzke H, Nagaraja R, Vollenweider P, Caulfield M, Illig T, Gieger C. Meta-analysis of 28,141 individuals identifies common variants within five new loci that influence uric acid concentrations. PLoS Genet. 2009; 5(6):e1000504. [PubMed: 19503597]

97. Brandstätter A, Lamina C, Kiechl S, Hunt S, Coassin S, Paulweber B, Kramer F, Summerer M, Willeit J, Kedenko L, Adams T, Kronenberg F. Sex and age interaction with genetic association of atherogenic uric acid concentrations. Atherosclerosis. 2009

98. Gafter-Gvili A, Ram R, Gafter U, Shpilberg O, Raanani P. Renal failure associated with tyrosine kinase inhibitors--case report and review of the literature. Leuk. Res. 2010; 34(1):123–127. [PubMed: 19640584]

99. Lin T, Ruppert A, Johnson A, Fischer B, Heerema N, Andritsos L, Blum K, Flynn J, Jones J, Hu W, Moran M, Mitchell S, Smith L, Wagner A, Raymond C, Schaaf L, Phelps M, Villalona-Calero

M, Grever M, Byrd J. Phase II study of flavopiridol in relapsed chronic lymphocytic leukemia demonstrating high response rates in genetically high-risk disease. J. Clin. Oncol. 2009; 27(35): 6012–6018. [PubMed: 19826119]

100. Huang W, Yang C. Sorafenib induced tumor lysis syndrome in an advanced hepatocellular carcinoma patient. World J. Gastroenterol. 2009; 15(35):4464–4466. [PubMed: 19764104]
101. Al-Kali A, Farooq S, Tfayli A. Tumor lysis syndrome after starting treatment with Gleevec in a patient with chronic myelogenous leukemia. J. Clin. Pharm. Ther. 2009; 34(5):607–610. [PubMed: 19744017]
102. de Figueiredo-Pontes L, Pintão M, Oliveira L, Dalmazzo L, Jácomo R, Garcia A, Falcão R, Rego E. Determination of P-glycoprotein, MDR-related protein 1, breast cancer resistance protein, and lung-resistance protein expression in leukemic stem cells of acute myeloid leukemia. Cytometry B Clin. Cytom. 2008; 74(3):163–168. [PubMed: 18200595]
103. Raaijmakers M, de Grouw E, Heuver L, van der Reijden B, Jansen J, Scheper R, Scheffer G, de Witte T, Raymakers R. Breast cancer resistance protein in drug resistance of primitive CD34+38- cells in acute myeloid leukemia. Clin. Cancer Res. 2005; 11(6):2436–2444. [PubMed: 15788695]
104. Ho M, Hogge D, Ling V. MDR1 and BCRP1 expression in leukemic progenitors correlates with chemotherapy response in acute myeloid leukemia. Exp. Hematol. 2008; 36(4):433–442. [PubMed: 18249061]
105. O'Brien CA, Kreso A, Jamieson C. Cancer stem cells and self-renewal. Clin. Cancer Res. 2010 in press.
106. Jiang X, Zhao Y, Smith C, Gasparetto M, Turhan A, Eaves A, Eaves C. Chronic myeloid leukemia stem cells possess multiple unique features of resistance to BCR-ABL targeted therapies. Leukemia. 2007; 21(5):926–935. [PubMed: 17330101]
107. Kanzaki A, Toi M, Nakayama K, Bando H, Mutoh M, Uchida T, Fukumoto M, Takebayashi Y. Expression of multidrug resistance-related transporters in human breast carcinoma. Jpn. J. Cancer Res. 2001; 92(4):452–458. [PubMed: 11346468]
108. Faneyte IF, Kristel PM, Maliepaard M, Scheffer GL, Scheper RJ, Schellens JH, van De Vijver MJ. Expression of the breast cancer resistance protein in breast cancer. Clin. Cancer. Res. 2002; 8(4):1068–1074. [PubMed: 11948115]
109. Burger H, Foekens JA, Look MP, Meijer-van Gelder ME, Klijn JG, Wiemer EA, Stoter G, Nooter K. RNA expression of breast cancer resistance protein, lung resistance-related protein, multidrug resistance-associated proteins 1 and 2, and multidrug resistance gene 1 in breast cancer: correlation with chemotherapeutic response. Clin. Cancer Res. 2003; 9(2):827–836. [PubMed: 12576456]
110. Yoh K, Ishii G, Yokose T, Minegishi Y, Tsuta K, Goto K, Nishiwaki Y, Kodama T, Suga M, Ochiai A. Breast cancer resistance protein impacts clinical outcome in platinum-based chemotherapy for advanced non-small cell lung cancer. Clin Cancer Res. 2004; 10(5):1691–1697. [PubMed: 15014021]
111. Ota S, Ishii G, Goto K, Kubota K, Kim Y, Kojika M, Murata Y, Yamazaki M, Nishiwaki Y, Eguchi K, Ochiai A. Immunohistochemical expression of BCRP and ERCC1 in biopsy specimen predicts survival in advanced non-small-cell lung cancer treated with cisplatin-based chemotherapy. Lung Cancer. 2009; 64(1):98–104. [PubMed: 18823676]
112. Kim Y, Ishii G, Goto K, Ota S, Kubota K, Murata Y, Mishima M, Saijo N, Nishiwaki Y, Ochiai A. Expression of breast cancer resistance protein is associated with a poor clinical outcome in patients with small-cell lung cancer. Lung Cancer. 2009; 65(1):105–111. [PubMed: 19036469]
113. Deeken J, Robey R, Shukla S, Steadman K, Chakraborty A, Poonkuzhali B, Schuetz E, Holbeck S, Ambudkar S, Bates S. Identification of compounds that correlate with ABCG2 transporter function in the National Cancer Institute Anticancer Drug Screen. Mol. Pharmacol. 2009; 76(5): 946–956. [PubMed: 19633067]
114. Kannan P, John C, Zoghbi S, Halldin C, Gottesman M, Innis R, Hall M. Imaging the function of P-glycoprotein with radiotracers: pharmacokinetics and in vivo applications. Clin. Pharmacol Ther. 2009; 86(4):368–377. [PubMed: 19625998]

115. Maitra R, Shaw C, Stanton B, Hamilton J. Increased functional cell surface expression of CFTR and DeltaF508-CFTR by the anthracycline doxorubicin. Am. J. Physiol. Cell Physiol. 2001; 280(5):C1031–C1037. [PubMed: 11287314]

116. Dormer R, Harris C, Clark Z, Pereira M, Doull I, Norez C, Becq F, McPherson M. Sildenafil (Viagra) corrects DeltaF508-CFTR location in nasal epithelial cells from patients with cystic fibrosis. Thorax. 2005; 60(1):55–59. [PubMed: 15618584]

117. Polgar O, Ediriwickrema L, Robey R, Sharma A, Hegde R, Li Y, Xia D, Ward Y, Dean M, Ozvegy-Laczka C, Sarkadi B, Bates S. Arginine 383 is a crucial residue in ABCG2 biogenesis. Biochim. Biophys. Acta. 2009; 1788(7):1434–1443. [PubMed: 19406100]

118. Polgar O, Robey RW, Morisaki K, Dean M, Michejda C, Sauna ZE, Ambudkar SV, Tarasova N, Bates SE. Mutational analysis of ABCG2: role of the GXXXG motif. Biochemistry. 2004; 43(29):9448–9456. [PubMed: 15260487]

119. Polgar O, Ierano C, Tamaki A, Stanley B, Ward Y, Xia D, Tarasova N, Robey R, Bates S. Mutational analysis of threonine 402 adjacent to the GXXXG dimerization motif in transmembrane segment 1 of ABCG2. Biochemistry. 2010; 49(10):2235–2245. [PubMed: 20088606]

120. Ebert B, Seidel A, Lampen A. Phytochemicals induce breast cancer resistance protein in Caco-2 cells and enhance the transport of benzo[a]pyrene-3-sulfate. Toxicol. Sci. 2007; 96(2):227–236. [PubMed: 17077187]

121. Maliepaard M, van Gastelen MA, de Jong LA, Pluim D, van Waardenburg RC, Ruevekamp-Helmers MC, Floot BG, Schellens JH. Overexpression of the BCRP/MXR/ABCP gene in a topotecan-selected ovarian tumor cell line. Cancer Res. 1999; 59(18):4559–4563. [PubMed: 10493507]

122. Brangi M, Litman T, Ciotti M, Nishiyama K, Kohlhagen G, Takimoto C, Robey R, Pommier Y, Fojo T, Bates SE. Camptothecin resistance: role of the ATP-binding cassette (ABC), mitoxantrone-resistance half-transporter (MXR), and potential for glucuronidation in MXR-expressing cells. Cancer Res. 1999; 59(23):5938–5946. [PubMed: 10606239]

123. Hiwase D, Saunders V, Hewett D, Frede A, Zrim S, Dang P, Eadie L, To L, Melo J, Kumar S, Hughes T, White D. Dasatinib cellular uptake and efflux in chronic myeloid leukemia cells: therapeutic implications. Clin. Cancer Res. 2008; 14(12):3881–3888. [PubMed: 18559609]

124. Ebert B, Seidel A, Lampen A. Identification of BCRP as transporter of benzo[a]pyrene conjugates metabolically formed in Caco-2 cells and its induction by Ah-receptor agonists. Carcinogenesis. 2005; 26(10):1754–1763. [PubMed: 15917307]

125. Jonker JW, Buitelaar M, Wagenaar E, Van Der Valk MA, Scheffer GL, Scheper RJ, Plosch T, Kuipers F, Elferink RP, Rosing H, Beijnen JH, Schinkel AH. The breast cancer resistance protein protects against a major chlorophyll-derived dietary phototoxin and protoporphyria. Proc. Natl. Acad. Sci. U. S. A. 2002; 99(24):15649–15654. [PubMed: 12429862]

126. Kato Y, Takahara S, Kato S, Kubo Y, Sai Y, Tamai I, Yabuuchi H, Tsuji A. Involvement of multidrug resistance-associated protein 2 (Abcc2) in molecular weight-dependent biliary excretion of beta-lactam antibiotics. Drug Metab. Dispos. 2008; 36(6):1088–1096. [PubMed: 18339814]

127. Fujino H, Saito T, Ogawa S, Kojima J. Transporter-mediated influx and efflux mechanisms of pitavastatin, a new inhibitor of HMG-CoA reductase. J. Pharm. Pharmacol. 2005; 57(10):1305–1311. [PubMed: 16259759]

128. Wu C, Shukla S, Calcagno A, Hall M, Gottesman M, Ambudkar S. Evidence for dual mode of action of a thiosemicarbazone, NSC73306: a potent substrate of the multidrug resistance linked ABCG2 transporter. Mol. Cancer Ther. 2007; 6(12 Pt 1):3287–3296. [PubMed: 18089722]

129. Bram E, Adar Y, Mesika N, Sabisz M, Skladanowski A, Assaraf Y. Structural determinants of imidazoacridinones facilitating antitumor activity are crucial for substrate recognition by ABCG2. Mol. Pharmacol. 2009; 75(5):1149–1159. [PubMed: 19251825]

130. Shukla S, Wu C, Nandigama K, Ambudkar S. The naphthoquinones, vitamin K3 and its structural analogue plumbagin, are substrates of the multidrug resistance linked ATP binding cassette drug transporter ABCG2. Mol. Cancer Ther. 2007; 6(12 Pt 1):3279–3286. [PubMed: 18065489]

131. van der Heijden J, de Jong MC, Dijkmans BA, Lems WF, Oerlemans R, Kathmann I, Schalkwijk CG, Scheffer GL, Scheper RJ, Jansen G. Development of sulfasalazine resistance in human T cells induces expression of the multidrug resistance transporter ABCG2 (BCRP) and augmented production of TNFalpha. Ann. Rheum. Dis. 2004; 63(2):138–143. [PubMed: 14722201]

132. Pavek P, Merino G, Wagenaar E, Bolscher E, Novotna M, Jonker JW, Schinkel AH. Human breast cancer resistance protein: interactions with steroid drugs, hormones, the dietary carcinogen 2-amino-1-methyl-6-phenylimidazo(4,5-b)pyridine, and transport of cimetidine. J. Pharmacol. Exp. Ther. 2005; 312(1):144–152. [PubMed: 15365089]

133. Gedeon C, Behravan J, Koren G, Piquette-Miller M. Transport of glyburide by placental ABC transporters: implications in fetal drug exposure. Placenta. 2006; 27(11–12):1096–1102. [PubMed: 16460798]

134. van Herwaarden AE, Wagenaar E, Merino G, Jonker JW, Rosing H, Beijnen JH, Schinkel AH. Multidrug transporter ABCG2/breast cancer resistance protein secretes riboflavin (vitamin B2) into milk. Mol. Cell. Biol. 2007; 27(4):1247–1253. [PubMed: 17145775]

135. Rabindran SK, Ross DD, Doyle LA, Yang W, Greenberger LM. Fumitremorgin C reverses multidrug resistance in cells transfected with the breast cancer resistance protein. Cancer Res. 2000; 60(1):47–50. [PubMed: 10646850]

136. Woehlecke H, Osada H, Herrmann A, Lage H. Reversal of breast cancer resistance protein-mediated drug resistance by tryprostatin A. Int. J. Cancer. 2003; 107(5):721–728. [PubMed: 14566821]

137. Qadir M, O'Loughlin KL, Fricke SM, Williamson NA, Greco WR, Minderman H, Baer MR. Cyclosporin A is a broad-spectrum multidrug resistance modulator. Clin. Cancer Res. 2005; 11(6):2320–2326. [PubMed: 15788683]

138. Gupta A, Dai Y, Vethanayagam RR, Hebert MF, Thummel KE, Unadkat JD, Ross DD, Mao Q. Cyclosporin A, tacrolimus and sirolimus are potent inhibitors of the human breast cancer resistance protein (ABCG2) and reverse resistance to mitoxantrone and topotecan. Cancer Chemother. Pharmacol. 2006; 58(3):374–383. [PubMed: 16404634]

139. Shi Z, Peng X, Kim I, Shukla S, Si Q, Robey R, Bates S, Shen T, Ashby CJ, Fu L, Ambudkar S, Chen Z. Erlotinib (Tarceva, OSI-774) antagonizes ATP-binding cassette subfamily B member 1 and ATP-binding cassette subfamily G member 2-mediated drug resistance. Cancer Res. 2007; 67(22):11012–11020. [PubMed: 18006847]

140. Houghton PJ, Germain GS, Harwood FC, Schuetz JD, Stewart CF, Buchdunger E, Traxler P. Imatinib mesylate is a potent inhibitor of the ABCG2 (BCRP) transporter and reverses resistance to topotecan and SN-38 in vitro. Cancer Res. 2004; 64(7):2333–2337. [PubMed: 15059881]

141. Dai C, Tiwari A, Wu C, Su X, Wang S, Liu D, Ashby CJ, Huang Y, Robey R, Liang Y, Chen L, Shi C, Ambudkar S, Chen Z, Fu L. Lapatinib (Tykerb, GW572016) reverses multidrug resistance in cancer cells by inhibiting the activity of ATP-binding cassette subfamily B member 1 and G member 2. Cancer Res. 2008; 68(19):7905–7914. [PubMed: 18829547]

142. Shukla S, Robey R, Bates S, Ambudkar S. Sunitinib (Sutent, SU11248), a small-molecule receptor tyrosine kinase inhibitor, blocks function of the ATP-binding cassette (ABC) transporters P-glycoprotein (ABCB1) and ABCG2. Drug Metab. Dispos. 2009; 37(2):359–365. [PubMed: 18971320]

143. Zheng L, Wang F, Li Y, Zhang X, Chen L, Liang Y, Dai C, Yan Y, Tao L, Mi Y, Yang A, To K, Fu L. Vandetanib (Zactima, ZD6474) antagonizes ABCC1- and ABCG2-mediated multidrug resistance by inhibition of their transport function. PLoS One. 2009; 4(4):e5172. [PubMed: 19390592]

144. Imai Y, Tsukahara S, Asada S, Sugimoto Y. Phytoestrogens/flavonoids reverse breast cancer resistance protein/ABCG2-mediated multidrug resistance. Cancer Res. 2004; 64(12):4346–4352. [PubMed: 15205350]

145. Weiss J, Rose J, Storch C, Ketabi-Kiyanvash N, Sauer A, Haefeli W, Efferth T. Modulation of human BCRP (ABCG2) activity by anti-HIV drugs. J. Antimicrob. Chemother. 2007; 59(2):238–245. [PubMed: 17202245]

146. Zhang Y, Gupta A, Wang H, Zhou L, Vethanayagam RR, Unadkat JD, Mao Q. BCRP transports dipyridamole and is inhibited by calcium channel blockers. Pharm. Res. 2005; 22(12):2023–2034. [PubMed: 16247709]

147. Yang CH, Chen YC, Kuo ML. Novobiocin sensitizes BCRP/MXR/ABCP overexpressing topotecan-resistant human breast carcinoma cells to topotecan and mitoxantrone. Anticancer Res. 2003; 23(3B):2519–2523. [PubMed: 12894535]

148. Chearwae W, Shukla S, Limtrakul P, Ambudkar SV. Modulation of the function of the multidrug resistance-linked ATP-binding cassette transporter ABCG2 by the cancer chemopreventive agent curcumin. Mol. Cancer Ther. 2006; 5(8):1995–2006. [PubMed: 16928820]

149. Robey RW, Shukla S, Steadman K, Obrzut T, Finley EM, Ambudkar SV, Bates SE. Inhibition of ABCG2-mediated transport by protein kinase inhibitors with a bisindolylmaleimide or indolocarbazole structure. Mol. Cancer Ther. 2007; 6(6):1877–1885. [PubMed: 17575116]

150. Sim H, Lee C, Ee P, Go M. Dimethoxyaurones: Potent inhibitors of ABCG2 (breast cancer resistance protein). Eur. J. Pharm. Sci. 2008; 35(4):293–306. [PubMed: 18725288]

151. Liu X, Tee H, Go M. Functionalized chalcones as selective inhibitors of P-glycoprotein and breast cancer resistance protein. Bioorg. Med. Chem. 2008; 16(1):171–180. [PubMed: 17964170]

152. Boumendjel A, Macalou S, Ahmed-Belkacem A, Blanc M, Di Pietro A. Acridone derivatives: design, synthesis, and inhibition of breast cancer resistance protein ABCG2. Bioorg. Med. Chem. 2007; 15(8):2892–2897. [PubMed: 17317193]

153. Holland M, Lau D, Allen J, Arnold J. The multidrug transporter ABCG2 (BCRP) is inhibited by plant-derived cannabinoids. Br. J. Pharmacol. 2007; 152(5):815–824. [PubMed: 17906686]

154. Ross DD, Karp JE, Chen TT, Doyle LA. Expression of breast cancer resistance protein in blast cells from patients with acute leukemia. Blood. 2000; 96(1):365–368. [PubMed: 10891476]

155. Sargent JM, Williamson CJ, Maliepaard M, Elgie AW, Scheper RJ, Taylor CG. Breast cancer resistance protein expression and resistance to daunorubicin in blast cells from patients with acute myeloid leukaemia. Br. J. Haematol. 2001; 115(2):257–262. [PubMed: 11703319]

156. van Der Kolk DM, Vellenga E, Scheffer GL, Muller M, Bates SE, Scheper RJ, De Vries EG. Expression and activity of breast cancer resistance protein (BCRP) in de novo and relapsed acute myeloid leukemia. Blood. 2002; 99(10):3763–3770. [PubMed: 11986234]

157. Sauerbrey A, Sell W, Steinbach D, Voigt A, Zintl F. Expression of the BCRP gene (ABCG2/MXR/ABCP) in childhood acute lymphoblastic leukaemia. Br. J. Haematol. 2002; 118(1):147–150. [PubMed: 12100141]

158. Abbott BL, Colapietro AM, Barnes Y, Marini F, Andreeff M, Sorrentino BP. Low levels of ABCG2 expression in adult AML blast samples. Blood. 2002; 100(13):4594–4601. [PubMed: 12393637]

159. Steinbach D, Sell W, Voigt A, Hermann J, Zintl F, Sauerbrey A. BCRP gene expression is associated with a poor response to remission induction therapy in childhood acute myeloid leukemia. Leukemia. 2002; 16(8):1443–1447. [PubMed: 12145683]

160. van Den Heuvel-Eibrink MM, Wiemer EA, Prins A, Meijerink JP, Vossebeld PJ, Van Der, Holt B, Pieters R, Sonneveld P. Increased expression of the breast cancer resistance protein (BCRP) in relapsed or refractory acute myeloid leukemia (AML). Leukemia. 2002; 16(5):833–839. [PubMed: 11986944]

161. van der Pol MA, Broxterman HJ, Pater JM, Feller N, van der Maas M, Weijers GW, Scheffer GL, Allen JD, Scheper RJ, van Loevezijn A, Ossenkoppele GJ, Schuurhuis GJ. Function of the ABC transporters, P-glycoprotein, multidrug resistance protein and breast cancer resistance protein, in minimal residual disease in acute myeloid leukemia. Haematologica. 2003; 88(2):134–147. [PubMed: 12604403]

162. Nakanishi T, Karp JE, Tan M, Doyle LA, Peters T, Yang W, Wei D, Ross DD. Quantitative analysis of breast cancer resistance protein and cellular resistance to flavopiridol in acute leukemia patients. Clin. Cancer Res. 2003; 9(9):3320–3328. [PubMed: 12960118]

163. Plasschaert SL, van der Kolk DM, de Bont ES, Kamps WA, Morisaki K, Bates SE, Scheffer GL, Scheper RJ, Vellenga E, de Vries EG. The role of breast cancer resistance protein in acute lymphoblastic leukemia. Clin. Cancer Res. 2003; 9(14):5171–5177. [PubMed: 14613996]

164. Stam RW, van den Heuvel-Eibrink MM, den Boer ML, Ebus ME, Janka-Schaub GE, Allen JD, Pieters R. Multidrug resistance genes in infant acute lymphoblastic leukemia: Ara-C is not a substrate for the breast cancer resistance protein. Leukemia. 2004; 18(1):78–83. [PubMed: 14574327]

165. Suvannasankha A, Minderman H, O'Loughlin KL, Nakanishi T, Greco WR, Ross DD, Baer MR. Breast cancer resistance protein (BCRP/MXR/ABCG2) in acute myeloid leukemia: discordance between expression and function. Leukemia. 2004; 18(7):1252–1257. [PubMed: 15208643]

166. Suvannasankha A, Minderman H, O'Loughlin KL, Nakanishi T, Ford LA, Greco WR, Wetzler M, Ross DD, Baer MR. Breast cancer resistance protein (BCRP/MXR/ABCG2) in adult acute lymphoblastic leukaemia: frequent expression and possible correlation with shorter disease-free survival. Br. J. Haematol. 2004; 127(4):392–398. [PubMed: 15521915]

167. Benderra Z, Faussat AM, Sayada L, Perrot JY, Chaoui D, Marie JP, Legrand O. Breast cancer resistance protein and P-glycoprotein in 149 adult acute myeloid leukemias. Clin. Cancer Res. 2004; 10(23):7896–7902. [PubMed: 15585622]

168. Uggla B, Stahl E, Wagsater D, Paul C, Karlsson MG, Sirsjo A, Tidefelt U. BCRP mRNA expression v. clinical outcome in 40 adult AML patients. Leuk. Res. 2005; 29(2):141–146. [PubMed: 15607361]

169. Galimberti S, Guerrini F, Palumbo GA, Consoli U, Fazzi R, Morabito F, Santini V, Petrini M. Evaluation of BCRP and MDR-1 co-expression by quantitative molecular assessment in AML patients. Leuk. Res. 2004; 28(4):367–372. [PubMed: 15109536]

170. Benderra Z, Faussat A, Sayada L, Perrot J, Tang R, Chaoui D, Morjani H, Marzac C, Marie J, Legrand O. MRP3, BCRP, and P-glycoprotein activities are prognostic factors in adult acute myeloid leukemia. Clin Cancer Res. 2005; 11(21):7764–7772. [PubMed: 16278398]

171. Wilson CS, Davidson GS, Martin SB, Andries E, Potter J, Harvey R, Ar K, Xu Y, Kopecky KJ, Ankerst DP, Gundacker H, Slovak ML, Mosquera-Caro M, Chen IM, Stirewalt DL, Murphy M, Schultz FA, Kang H, Wang X, Radich JP, Appelbaum FR, Atlas SR, Godwin J, Willman CL. Gene expression profiling of adult acute myeloid leukemia identifies novel biologic clusters for risk classification and outcome prediction. Blood. 2006; 108(2):685–696. [PubMed: 16597596]

172. Damiani D, Tiribelli M, Calistri E, Geromin A, Chiarvesio A, Michelutti A, Cavallin M, Fanin R. The prognostic value of P-glycoprotein (ABCB) and breast cancer resistance protein (ABCG2) in adults with de novo acute myeloid leukemia with normal karyotype. Haematologica. 2006; 91(6): 825–828. [PubMed: 16704962]

173. van den Heuvel-Eibrink M, van der Holt B, Burnett A, Knauf W, Fey M, Verhoef G, Vellenga E, Ossenkoppele G, Löwenberg B, Sonneveld P. CD34-related coexpression of MDR1 and BCRP indicates a clinically resistant phenotype in patients with acute myeloid leukemia (AML) of older age. Ann. Hematol. 2007; 86(5):329–337. [PubMed: 17340137]

174. Kourti M, Vavatsi N, Gombakis N, Sidi V, Tzimagiorgis G, Papageorgiou T, Koliouskas D, Athanassiadou F. 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. Int. J. Hematol. 2007; 86(2):166–173. [PubMed: 17875533]

175. Shman T, Fedasenka U, Savitski V, Aleinikova O. CD34+ leukemic subpopulation predominantly displays lower spontaneous apoptosis and has higher expression levels of Bcl-2 and MDR1 genes than CD34- cells in childhood AML. Ann. Hematol. 2008; 87(5):353–360. [PubMed: 18228020]

176. Fedasenka U, Shman T, Savitski V, Belevcev M. Expression of MDR1, LRP, BCRP and Bcl-2 genes at diagnosis of childhood all: comparison with MRD status after induction therapy. Exp. Oncol. 2008; 30(3):248–252. [PubMed: 18806751]

177. Cortez M, Scrideli C, Yunes J, Valera E, Toledo S, Pavoni-Ferreira P, Lee M, Petrilli A, Brandalise S, Tone L. mRNA expression profile of multidrug resistance genes in childhood acute lymphoblastic leukemia. Low expression levels associated with a higher risk of toxic death. Pediatr. Blood Cancer. 2009; 53(6):996–1004. [PubMed: 19672972]

178. Svirnovski A, Shman T, Serhiyenka T, Savitski V, Smolnikova V, Fedasenka U. ABCB1 and ABCG2 proteins, their functional activity and gene expression in concert with drug sensitivity of leukemia cells. Hematology. 2009; 14(4):204–212. [PubMed: 19635183]

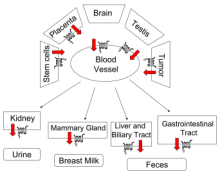

Figure 1.
Schematic representation of ABCG2 expression in normal tissues. Arrows indicate direction of substrate transport. In the brain and testis, ABCG2 is expressed mainly in the blood vessel endothelium, forming part of the blood-brain and blood-testis barrier, respectively.

Table 1

Select substrates of ABCG2

Mitoxantrone[1]
Camptothecins
Topotecan[121]
Irinotecan (and SN-38)[122]
9-aminocamptothecin[19]
Tyrosine Kinase Inhibitors
Imatinib[28]
Gefitinib[27]
Nilotinib[29]
Dasatinib[123]
Carcinogens
Aflatoxin B1[37]
Benzo[a]pyrene sulfate[124]
2-amino-3-methylimidazo[4,5-f]quinoline (IQ)[37]
3-amino-1,4-dimethyl-5H-pyrido[4,3-b]indole (Trp-P-1)[37]
2-amino-1-methyl-6-phenylimidazo(4,5-b)pyridine (PhIP)[36]
Porphyrins and Photosensitizers
Pheophorbide a[125]
Pyropheophorbide a methyl ester[26]
Chlorin e6[26]
Protoporphyrin IX[25]
Benzoporphyrin derivative monoacid ring A[25]
2-[1-Hexyloxyethyl]-2 Devinyl Pyropheophorbide-a (HPPH)[25]
Antibiotics
Cephalosporins[126]
Fluoroquinolones[35]
Antifolates[23, 24]
HMG-CoA reductase inhibitors[32, 127]
Thiosemicarbazones[113, 128]
Imidazoacridinones[129]
Naphthoquinones[130]
Pancratistatin[113]
Sulfasalazine[131]
Cimetidine[132]
Flavopiridol[16]
Uric Acid[31]
Glyburide[133]
Becatecarin[22]

Riboflavin[134]

Table 2

Select inhibitors of ABCG2

Diketopiperazines
Fumitremorgin C[135]
Ko143[73]
Tryprostatin A[136]
Immunosupressants
Cyclosporin A[137]
Tacrolimus[138]
Sirolimus[138]
Tyrosine Kinase Inhibitors
Gefitinib[46]
Erlotinib[139]
Imatinib[140]
Nilotinib[29]
Lapatinib[141]
Sunitinib[142]
Vandetanib[143]
P-glycoprotein Inhibitors
Elacridar[41]
Tariquidar[44]
Biricodar[42]
Dofequidar[43]
Flavonoids
Genistein[144]
Naringenin[144]
Kaempferol[144]
Chrysin[47]
6-prenylchrysin[48]
Antivirals[145]
Calcium Channel Blockers[146]
Botryllamides[50]
Novobiocin[147]
Curcumin[148]
Bisindolylmaleimides[149]
Indolocarbazoles[149]
Dimethoxyaurones[150]
Chalcone Derivatives[151]
Acridone Derivatives[152]
Nonprenylated Rotenoids[49]

Cannabinoids[153]

Table 3

Leukemia studies examining ABCG2 expression

Author	Cancer	Method	Samples	Conclusion
Ross et al 2000[154]	AML ALL	RT-PCR	20 AML samples 1 ALL sample	High ABCG2 levels in 33% of samples.
Sargent et al 2001[155]	AML	IHC: BXP-34 antibody	20 AML samples	27% of samples had >10% of cells stain positive.
van der Kolk et al 2002 [156]	AML	FC: BXP-21, mitoxantrone transport	20 paired de novo and relapsed/refractory AML samples	Higher ABCG2 protein levels and lower mitoxantrone accumulation in CD34+CD33- cells; lower expression and higher mitoxantrone accumulation in CD34-CD33+ cells
Sauerbrey et al 2002[157]	Childhood ALL	RT-PCR	47 de novo childhood ALL samples 20 relapsed childhood ALL samples	No correlation between ABCG2 expression and response.
Abbott et al 2002[158]	AML	RT-PCR	40 de novo AML samples	Intermediate to high levels of ABCG2 in 83% of samples.
Steinbach et al 2002[159]	Childhood AML	RT-PCR	59 de novo AML	In non-remission group, *ABCG2* levels were 10- fold higher compared to remission group. In 9 patients with initial stage and relapse samples, ABCG2 higher at relapse.
van den Heuvel-Eibrink et al 2002[160]	AML	RT-PCR	20 paired de novo and relapsed/refractory AML samples	*ABCG2* levels higher at relapse than at diagnosis.
van der Pol et al 2003 [161]	AML	FC: BXP-21, BXP-34, BODIPY-prazosin transport	45 AML patients	No changes in ABCG2 expression or function at relapse.
Nakanishi et al 2003[162]	Acute Leukemia	RT-PCR	21 AML samples	ABCG2 expression in blast samples correlated with in vitro resistance to flavopiridol.
Plasschaert et al 2003 [163]	ALL	FC: BXP-34, mitoxantrone transport	46 de novo ALL samples	Higher ABCG2 expression and function in B-cell lineage ALL.
Stam et al 2004[164]	Childhood ALL	RT-PCR	26 de novo ALL samples	ABCG2 expression significantly less in infants compared to older children.
Suvannasankha et al 2004[165]	AML	RT-PCR FC: BXP-21, BXP-34, 5D3, mitoxantrone transport	31 pretreatment blast samples	Increased 5D3 staining correlated with decreased probablility of achieving CR.
Suvannasankha et al 2004[166]	ALL	RT-PCR FC: BXP-21, BXP-34, 5D3, mitoxantrone transport	30 de novo ALL samples	Significant correlation between BXP-21 staining and shorter DFS.
Benderra et al 2004[167]	AML	RT-PCR	149 de novo AML samples	ABCG2 expression was prognostic factor of CR, 4-year DFS and 4-year overall survival. Predictive in patients receiving daunorubicin, and mitoxantrone but not idarubicin.
Uggla et al 2005[168]	AML	RT-PCR	40 de novo AML samples	Of responders, patients with lower ABCG2 expression had longer survival than patients with

Author	Cancer	Method	Samples	Conclusion
				high ABCG2 expression.
Galimberti et al 2005[169]	AML	RT-PCR	51 de novo AML samples	ABCG2 expression was found in 56% of samples; 48.2% had intermediate levels 27.6% had high levels.
Raaijmakers et al 2005[103]	AML	RT-PCR FC: BXP-21, mitoxantrone Transport	22 de novo AML samples	Highest ABCG2 protein and function in most primitive CD34+CD38- AML population versus more differentiated CD34+CD38+ and CD34- populations.
Benderra et al 2005[170]	AML	FC: BXP-34, mitoxantrone transport	85 de novo AML samples	ABCG2 function correlated with prognosis and was higher in non-responders and in patients with poor DFS and poor OS. Higher ABCG2 function associated with lower CR rate.
Wilson et al 2006[171]	AML			
Damiani et al 2006[172]	AML	FC: BXP-34	73 de novo AML samples with normal karyotype	ABCG2 protein overexpressed in 33% of samples
van den Heuvel-Eibrink 2007[173]	AML of older age	RT-PCR	154 de novo AML samples	Higher ABCG2 expression associated with secondary AML. ABCG2 expression associated with ABCB1 expression. CD-34 related ABCB1/ABCG2 coexpression significantly associated with a lower CR rate.
Kourti et al 2007[174]	Childhood ALL	RT-PCR	31 bone marrow samples	High ABCG2 expression in 32% of samples.
Jiang et al 2007[106]	CML	RT-PCR	18 CML samples	Lin-CD34+CD38-cells express high *ABCG2* *ABCB1* and low *OCT1*.
de Figueiredo-Pontes et al 2008[102]	AML	FC: BXP-21	26 de novo AML samples	Higher ABCG2 expression in leukemic stem cells (CD34CD38-CD123+) versus more mature (CD34+CD38+) cells.
Shman et al 2008[175]	Childhood AML	RT-PCR	29 childhood AML samples	Higher *ABCG2* expression in CD34+ cells.
Ho et al 2008[104]	AML	RT-PCR	31 de novo AML samples	No difference in ABCG2 expression in total blasts from patients achieving CR versus NR, but higher ABCG2 expression in CD34+CD38- AML subset in NR versus CR samples.
Fedasenka et al 2008[176]	Childhood ALL	RT-PCR	19 childhood B-cell ALL samples	*ABCG2* levels lower in patients with minimal residual disease but not statictically significant.
Cortez et al 2009[177]	Childhood ALL	RT-PCR	118 de novo B-cell ALL 22 de novo T-cell ALL	*ABCG2* expression in the whole population and *ABCG2* and *ABCC1* expression in high-risk group associated with PFS. Low *ABCG2* expression

Author	Cancer	Method	Samples	Conclusion
				associated with higher treatment-related death in the whole population and low *ABCG2* and *ABCC1* expression related to treatment-related death in high-risk group.
Svirnovski et al 2009[178]	Pediatric ALL, AML Adult CLL	Semi-quantitative RT-PCR FC: BXP-21, mitoxantrone transport	65 de novo Childhood ALL 42 relapse Childhood ALL 53 de novo Childhood AML 16 relapse Childhood AML 16 de novo adult CLL 23 treated adult CLL	Low ABCG2 protein expression in pediatric acute leukemias and adult CLL. Functional ABCG2 in 100% of relapsed ALL, 33% of de novo AML, 17% of relapsed AML and 50% of CLL samples. No difference in *ABCG2* expression between de novo and relapsed samples.

Table 4

Relative ABCG2 gene expression in unselected and drug-selected cancer cell lines.

Cell line	ABCG2 expression
MCF-7	10
MCF-7 FLV100	535.2
MCF-7 FLV250	592.8
MCF-7 FLV500	783.2
MCF-7 FLV1000	1837.6
SF295	41.8
NCI-H460	264
A549	115.8
HCC-2998	52.3

Gene expression was determined by RT-PCR analysis and normalized to the level of expression in MCF-7 parental cells, arbitrarily assigned a value of 10 units. MCF-7 FLV100, 250, 500 and 1000 cells are maintained in 100, 250, 500 and 1000 nM flavopiridol, respectively. MCF-7 AdVp3000 cells are maintained in 3000 ng/ml adriamycin with 2.5 μM verapamil.