Molecular Pharmacology Fast Forward. Published on July 23, 2012 as doi: 10.1124/mol.112.079129

MOL #79129

Drug efflux transporters and multidrug resistance in acute leukemia: therapeutic impact and novel approaches to mediation

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Molecular Pharmacology Fast Forward. Published on July 23, 2012 as DOI: 10.1124/mol.112.079129
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Running title: Efflux transporters and multidrug resistance in leukemia

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Number of text pages: 18

Number of tables: 2

Number of figures: 1

Number of references: 211

Abstract word count: 237 words

Body text word count: 6929 words

ABBREVIATIONS

ABC – ATP-binding cassette

ALL – acute lymphoblastic leukemia

AML – acute myeloid leukemia

BCRP – breast cancer resistance protein

COX – cyclo-oxygenase

CR – complete remission

EFS – event-free survival

EORTC – European Organization for the Research and Treatment of Cancer

GCS – glucosylceramide synthase

GST – glutathione S-transferase

HDAC – histone deacetylase inhibitor

LRP – lung resistance protein

MDR – multidrug resistance

MDS – myelodysplastic syndromes

MRP – multidrug resistance-associated protein

OS – overall survival

PET – positron emission tomography

P-gp – permeability glycoprotein

PFS – progression-free survival

shRNA – short hairpin RNA

siRNA – small interfering RNA

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SNP – single nucleotide polymorphism

SPECT – single-photon emission computed tomography

SWOG – Southwest Oncology Group

TTP – time to progression

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ABSTRACT

Multidrug resistance (MDR), mediated by multiple drug efflux ATP-binding cassette (ABC) transporters, is a critical issue in the treatment of acute leukemia, with permeability (P)-glycoprotein (P-gp), multidrug resistance-associated protein 1 (MRP1), and breast cancer resistance protein (BCRP, or ABCG2) consistently shown to be the key effectors of MDR in cell line studies. Studies have demonstrated that intrinsic MDR can arise due to specific gene expression profiles, and that drug-induced overexpression of P-gp and other MDR proteins can result in acquired resistance, with multiple ABC transporters having been shown to be overexpressed in cell lines selected for resistance to multiple drugs for acute leukemia. Further, numerous anticancer drugs, including agents commonly used in the treatment of acute leukemia, such as doxorubicin, vincristine, mitoxantrone, and methotrexate, have been shown to be P-gp substrates or to be susceptible to efflux via other MDR proteins, and multiple clinical studies have demonstrated associations between P-gp or other MDR protein expression and response to therapy or survival in acute leukemia. Here we review the importance of MDR in cancer, with a focus on acute leukemia, and highlight the need for rapid, accurate assessment of MDR status for determining optimal treatment selection. We also address the latest research into overcoming MDR, from inhibition of P-gp and other MDR proteins via various approaches including direct antagonism and gene silencing, to designing novel agents or novel delivery systems for existing therapeutic agents to evade cellular efflux.

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INTRODUCTION

Drug resistance is a critical issue in the treatment of cancer, notably acute leukemias. Research over the past 25 years has shown that this resistance may be mediated by multiple multidrug resistance (MDR) proteins, with 48 ATP-binding cassette (ABC) transporters having been identified as facilitating the efflux of various substrates, including anticancer drugs, from cells (Steinbach and Legrand, 2007). Permeability (P)-glycoprotein (P-gp) was initially identified as the first ABC transporter associated with drug resistance (Campos et al., 1992; Kartner et al., 1983), but since then multiple additional transporters have been identified that confer resistance to a wide range of drugs (Szakacs et al., 2004). The three most studied MDR proteins are P-gp (encoded by the *MDR1* gene), multidrug resistance-associated protein 1 (MRP1), and breast cancer resistance protein (BCRP, or ABCG2), which have been consistently shown in cancer cell line studies to mediate the primary mechanism of MDR (Ambudkar et al., 1999; Abbott, 2003; Hipfner et al., 1999; Szakacs et al., 2004). The genes responsible for encoding these proteins, as well as other genes encoding additional ABC transporters known to be involved in anticancer drug resistance, are shown in Table 1, along with the known drug substrates of each MDR protein (Szakacs et al., 2006; Moitra et al., 2011). Other non-ABC transporter proteins with known roles in MDR are also listed. The 48 genes encoding the ABC transporters are subdivided into seven families, A–G, and, as shown in Table 1, a large number of proteins encoded by the B and C families in particular have been shown to confer resistance through efflux, highlighting their importance in cancer (Dean et al., 2001).

A number of studies have demonstrated that intrinsic MDR can arise due to specific gene expression profiles. For example, increased MDR gene expression (*MDR1* and *ABCG2*) was associated with poorer overall survival (OS) in a gene expression profiling study of adults with acute myeloid leukemia (AML) (Wilson et al., 2006). Interestingly, elevated P-gp expression has been identified more frequently in older versus younger AML patients (Erba, 2007), reflecting the greater resistance to therapy and the poorer prognosis seen in older AML patients. Given the importance of MDR gene expression, the contribution of genetic polymorphisms to intrinsic MDR has also been extensively investigated to determine whether a specific genotype or haplotype is associated with response to therapy (Leschziner et al., 2007). Individual studies have evaluated specific *MDR1* polymorphisms and P-gp expression in acute leukemias, with inconsistent results. In one study, there was no significant effect on P-gp-mediated drug resistance in acute leukemia patients associated with any of the

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C3435T, G2677T, or T-129C *MDR1* polymorphisms (Kaya et al., 2005), while in other studies C3435T polymorphisms were associated with poor prognosis in childhood, but not adult, acute lymphoblastic lymphoma, and not in adult AML (Jamroziak et al., 2004; Jamroziak et al., 2005; Jamroziak et al., 2006). However, in another study, the C/C and G/G genotypes of C3435T were associated with a higher probability of complete remission and longer event-free survival (EFS) (Kim et al., 2006). Further work is required in this area (Leschziner et al., 2007).

Additional studies have demonstrated that drug-induced overexpression of P-gp and other MDR proteins can result in acquired resistance, with multiple ABC transporters being overexpressed in cell lines selected for resistance to multiple AML drugs (Ambudkar et al., 1999; Szakacs et al., 2006). For example, doxorubicin induces overexpression of MDR1 in HL-60 AML cells (Puhlmann et al., 2005), and upregulated expression of both *MDR1* and *MRP1* has been demonstrated in doxorubicin-resistant HL-60 cells (HL-60/DOX) (Baran et al., 2007). Similarly, cytarabine was shown to upregulate *MDR1* gene and P-gp protein expression in HL-60 cells (Prenkert et al., 2009).

The current review addresses the important issue of MDR in AML and other cancers, and highlights the critical need for rapid, accurate assessment of MDR status for determining optimal treatment selection, based upon known resistance to various agents. We discuss the specific aspects of MDR status and their prognostic significance in AML and other cancers, and also address the latest research into overcoming MDR, from P-gp inhibition to designing novel agents to evade cellular efflux.

ASSESSMENT OF MDR STATUS

Numerous anticancer drugs, including agents commonly used in the treatment of acute leukemia, such as doxorubicin, vincristine, mitoxantrone, and methotrexate, have been shown to be P-gp substrates or to be susceptible to efflux via other MDR proteins (Table 1). It is thus important to assess MDR status, to inform appropriate treatment selection. Multiple methods have been investigated for assessing MDR in cell lines and in patients, with various recent developments offering the potential for accurate identification of gene overexpression or protein upregulation.

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For example, semi-quantitative RT-PCR has been used in studies for analysis of *MDR1* expression in patients with AML (Balatzenko et al., 2002; Trnkova et al., 2007), and, while higher expression in the bone marrow correlated with lower complete remission (CR) induction in one study, there was no association with OS (Trnkova et al., 2007). RT-PCR with fluorescent hybridization probes has also been used to evaluate the expression of *BCRP* in patients with acute leukemia (Nakanishi et al., 2003). Further, rapid detection of P-gp, MRP1, and BCRP has been demonstrated using a technique based on an automated cell counter with fluorescence detection capability (Robey et al., 2011), while BCRP and MRP2 activity have been assessed using membrane vesicle-based assays (Elsby et al., 2011) and MRP1 expression has been analyzed via a capillary electrophoresis immunoassay (Mbuna et al., 2011). In addition, a novel technique – reverse-phase protein microarray assay – for identifying MDR leukemia cells based upon Akt1 activity or phosphorylation has been reported, with higher Akt1 activity demonstrated in MDR cells (Maraldi et al., 2011). Other novel techniques studied for assessing P-gp-mediated transport activity include the use of gallium-labeled metalloprobes (Sivapackiam et al., 2010) and single-photon emission computed tomography (SPECT) with other radiolabeled metal complexes (Piwnica-Worms and Sharma, 2010).

Among older techniques, fluorometric assay of calcein accumulation or uptake, in conjunction with flow cytometry, provides a method of measuring P-gp functional activity, as calcein is effluxed by P-gp and thus uptake is significantly lower in P-gp-expressing cells compared with controls (Hollo et al., 1994; Homolya et al., 1996). This technique has been used to demonstrate the correlation between P-gp and MRP1 expression and activity in pediatric acute lymphoblastic leukemia (ALL) and adult AML (Fazlina et al., 2008; Legrand et al., 1998). Indeed, low calcein uptake has been shown to be a marker of poor prognosis in AML (Legrand et al., 1998). MDR in AML patients has also be assessed using efflux assays of rhodamine 123 (Lamy et al., 1995), JC-1 (Legrand et al., 2001), $Di(OC)_2$ (Leith et al., 1999), and daunorubicin (Kim et al., 2005), all substrates of P-gp, as well as with the MDR1-specific antibody MRK16 (Leith et al., 1997). Notably, higher daunorubicin efflux was significantly predictive of lower CR rate and poorer OS in patients with AML, and more reliable than *MDR1* RT-PCR or P-gp expression (Kim et al., 2005), indicating the importance of evaluating functional activity rather than gene or protein expression alone. Rhodamine 123 efflux correlated with P-gp expression, and both were predictive for CR rate and OS in AML/ALL patients; however, some patients showed efflux without

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P-gp expression, indicating the importance of other MDR efflux pumps (Lamy et al., 1995).

Positron emission tomography (PET) using ^{18}F-fluoroethyl compounds (Kawamura et al., 2011) and (99m)Tc MIBI scintigraphy (Dizdarevic and Peters, 2011) have also recently been used to assess the *in vivo* function of P-gp and BCRP, while another study suggested that MDR could be determined using a carbon nanotube-drug supramolecular nanocomposite electrochemical sensor, as demonstrated with sensitive and MDR K562 leukemia cells (Zhang et al., 2011a). Finally, as noted recently, the combination of SPECT, PET, and other imaging techniques with genetic data, informed by the findings of preclinical and clinical studies of MDR, may prove important for selecting optimal treatment for patients demonstrating particular MDR phenotypes (Dizdarevic and Peters, 2011).

Among the methods highlighted here, RT-PCR represents the most convenient assay for assessing MDR gene expression. However, it remains difficult to correlate differences in the magnitude of MDR mRNA expression with differences in MDR protein levels or function. Although a protein microarray assay is now available, more data are required to demonstrate a relationship between protein level and functionality. The cell-based functional assays, such as rhodamine 123 and doxorubicin efflux, and the fluorescent cell-count and membrane vesicle-based assays can directly reflect MDR activity but present some technical challenges associated with preparing live cells or membrane vesicles. The *in vivo* imaging assay offers the best indication of the clinical significance of MDR; however, its broad utilization remains challenging due to the availability of imaging agents. Overall, given the limitations associated with each method, a recommendation might be to use multiple assays, and, until definitive links between assays and activity are demonstrated, to interpret findings with caution.

MDR PROTEINS CONFER RESISTANCE IN PRECLINICAL IN VITRO MODELS

Numerous *in vitro* studies have highlighted the importance of P-gp in AML resistance (Pallis et al., 2002). P-gp has been associated with resistance to a range of drugs in AML cell lines (Table 1), and it has been suggested that P-gp plays a role in the development of an apoptosis-resistant phenotype (Pallis et al., 2002; Guenova et al., 2010). For example, as noted earlier, *MDR1* expression has been shown to be upregulated in doxorubicin-resistant HL-60/DOX AML cells (Baran et al., 2007), and

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to be associated with *in vitro* sensitivity to daunorubicin in cells from adults with acute leukemia (Marie et al., 1991). Similarly, P-gp overexpression resulted in resistance to gemtuzumab ozogamicin in HL-60 cells (Cianfriglia et al., 2010) as well as in reduced sensitivity to FLT3 inhibitors in FLT3-ITD-positive primary AML blasts (Hunter et al., 2004), while P-gp activity was also identified as a possible mechanism mediating sensitivity of leukemia cell lines to 17-AAG (Napper and Sollars, 2010). In studies of 13 cell lines, including some leukemic cell lines, P-gp expression was associated with the inhibitory effects of cyclosporine A on rhodamine 123, daunorubicin, and calcein-AM uptake (Legrand et al., 1998), while P-gp overexpression in ALL cells was also associated with resistance to silvestrol, a translation initiation inhibitor (Gupta et al., 2011). Clofarabine cytotoxicity in AML cells was shown to be reduced by P-gp efflux, which was in turn mediated by deoxycytidine kinase; deoxycytidine kinase is responsible for clofarabine activation through monophosphorylation, and P-gp effluxed clofarabine more readily than its monophosphate (Nagai et al., 2011).

In contrast to the above findings for *MDR1* expression, an analysis of blast cell samples from acute leukemia patients showed that *BCRP* but not *MDR1* expression correlated with cell viability to and induction of apoptosis by flavopiridol (Nakanishi et al., 2003). In another report, *BCRP* along with other transporters was shown to mediate drug efflux in leukemic cell line studies (Raaijmakers et al., 2005). As with P-gp, multiple studies have shown that expression of MRP1 is associated with resistance in AML cell lines. For example, studies in MRP-positive NB4 and HL-60 cells showed that gemtuzumab ozogamicin-induced cytotoxicity is attenuated by MRP1 expression (Walter et al., 2003). Further, MRP1 expression was shown to reduce DNA intercalation of daunorubicin and idarubicin (Smeets et al., 1999) and to be upregulated in AML-2/DX300 (Kweon et al., 2010) and HL60/DOX (Baran et al., 2007) doxorubicin-resistant AML cells. MRP1 was also found to be overexpressed in an arsenic trioxide-resistant human leukemia cell line, K562/AS-3 (Seo et al., 2007). Additionally, MRP4 has been shown to potentially play a role in AML cell proliferation and differentiation through the efflux of cAMP, which plays a key role in cell maturation (Copsel et al., 2011). By contrast, studies of pediatric ALL and AML cells have not demonstrated a definitive link between P-gp and BCRP expression and drug resistance *in vitro* (Svirnovski et al., 2009). However, studies with leukemia cell lines and SCID mouse xenograft models demonstrated that P-gp overexpression may be associated with enhanced leukemic cell invasiveness (Hu et al., 2011).

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IMPACT OF MDR EXPRESSION ON CLINICAL OUTCOMES

MDR in acute myeloid leukemia and other acute leukemias

Several clinical studies have demonstrated an association between P-gp expression, or P-gp function/activity, and response to therapy or survival in AML and other acute leukemias (Pallis et al., 2002; Trnkova et al., 2007). *MDR1* expression has been evaluated in a number of studies. Huh et al demonstrated poorer 2-year survival in ALL and AML patients with high *MDR1* mRNA expression (Huh et al., 2006); reduced response to induction therapy was also seen among those with high *MDR1* expression in another study of adult acute leukemia patients (Marie et al., 1991), while in an analysis of 331 adult AML patients, *MDR1* expression was prognostic for poorer outcome to induction therapy and shorter OS (Schaich et al., 2005), and in an analysis of 49 pediatric ALL patients high *MDR1* expression was associated with significantly poorer EFS (Kourti et al., 2007). *MDR1* expression was also associated with lower CR rate, but not decreased OS, in a study of 405 AML patients (Illmer et al., 2002); the specific homozygous wild-type genotype was associated with decreased OS and increased risk of relapse, suggesting additional mechanisms are involved other than P-gp expression alone (Illmer et al., 2002). Furthermore, an analysis of *MDR1* expression and FLT3-ITD mutation status in 166 adult AML patients demonstrated shorter time to relapse in *MDR1* overexpressing patients, and poor disease-free survival in patients with both *MDR1* overexpression and FLT3-ITD-positive status (Tiribelli et al., 2011).

The parameter of P-gp expression has also been shown to be associated with response and outcomes. P-gp expression was associated with significantly lower CR rate, as well as resistant disease, in elderly patients with AML enrolled in a SWOG study (Leith et al., 1997), and P-gp expression level was also prognostic for OS in an analysis of 121 adults with *de novo* AML (Wuchter et al., 2000). P-gp expression was also prognostic for not achieving CR among 53 AML patients treated in two EORTC study protocols (Legrand et al., 1998), and was associated with a lower CR rate in an analysis of 200 adult ALL patients (Tafuri et al., 2002). Venditti et al demonstrated that newly diagnosed AML patients who expressed both Bcl-2 and P-gp had a significantly lower CR rate to standard induction therapy than patients expressing only one or neither of these proteins (Venditti et al., 2004). As noted earlier, a higher proportion of older versus younger AML patients have MDR and an anti-apoptotic phenotype, which is associated with a higher incidence of homogeneous CD34+ blast cell populations in older patients – these blast cells show elevated P-gp and Bcl-2 expression (Suarez et al., 2005). Elevated expression of P-gp and Bcl-2 has

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also been reported in CD34+ versus CD34- childhood AML leukemic cells (Shman et al., 2008). Furthermore, P-gp expression on the surface of acute non-lymphoblastic lymphoma cells taken at diagnosis was associated with significantly lower CR rate and shorter survival in an analysis of 150 patients (Campos et al., 1992). Similarly, P-gp activity, identified using rhodamine efflux assay, was associated with significantly shorter OS in pediatric ALL in one study (Brozek et al., 2009), and with response to induction, relapse rate, and OS in adult AML, but not newly diagnosed pediatric ALL, in another analysis (Wuchter et al., 2000).

P-gp is not the only MDR transporter to be associated with poorer response to therapy and survival in acute leukemia. Multiple studies have associated *BCRP* gene expression, and BCRP protein expression and/or function, with poor response and prognosis in adult (Benderra et al., 2004; Benderra et al., 2005; Damiani et al., 2006; Uggla et al., 2005) and pediatric (Steinbach et al., 2002) AML; a recent study has shown that the adverse impact of BCRP on disease-free survival is not overcome with fludarabine-based induction therapy (Damiani et al., 2010). In older AML patients, co-expression of MDR1 and BCRP was shown to be associated with a clinically resistant phenotype (Van den Heuvel-Eibrink et al., 2007), and, similarly, elevated expression of MDR1 and/or BCRP in CD34+/CD38- AML cells correlated with negative response to chemotherapy in patients and at the cellular level (Ho et al., 2008).

In contrast to other findings (Laupeze et al., 2002; Legrand et al., 1998; Schaich et al., 2005), a number of studies have not demonstrated a prognostic impact of *MRP1* expression in AML (Leith et al., 1999; van der Kolk et al., 2000). Additionally, *MRP1*, *MRP2*, *MRP3*, *MRP5*, and *MRP6* expression were all shown to be associated with poorer relapse-free survival in pediatric and adult ALL (Plasschaert et al., 2005). In other studies, *MRP3* expression was also associated with poor prognosis in pediatric ALL (Steinbach et al., 2003b), and pediatric (Steinbach et al., 2003a) and adult AML (Benderra et al., 2005). Lung resistance protein (LRP) expression has also been associated with therapeutic efficacy; List et al demonstrated that LRP overexpression was associated with poorer response to induction therapy and a trend towards shorter duration of response and OS in an analysis of 66 AML patients (List et al., 1996), while Huh et al showed that *LRP* mRNA expression was associated with resistance to induction chemotherapy in acute leukemia patients, *MRP1* mRNA expression was associated with poorer 2-year survival, and expression of both *MRP1* and *LRP* identified patients with very poor 2-year survival (Huh et al., 2006). Similar

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findings were reported from an analysis of 34 pediatric ALL patients, with *MRP1* and *LRP* mRNA expression being associated with lower CR rates and poorer 2-year survival (El-Sharnouby et al., 2010). Finally, a phase 2 study of gemcitabine and mitoxantrone in AML patients at first relapse suggested that higher expression of total MRP4 and SLC29A2 (solute carrier family) was associated with not achieving CR (Advani et al., 2010); high expression of glutathione S-transferase P (encoded by GSTP1) was also seen (Advani et al., 2010).

Prognostic impact of specific MDR gene polymorphisms in acute leukemias

With numerous studies demonstrating the adverse prognostic impact of upregulated *MDR1* transcription or P-gp expression/activity in AML and other acute leukemias, multiple analyses have been undertaken to determine whether specific *MDR1* gene polymorphisms are associated with poorer response to treatment and overall outcome, with mixed findings (Leschziner et al., 2007), as summarized in Table 2. A number of studies have reported positive associations between specific *MDR1* polymorphisms and response and/or outcome (Monzo et al., 2006; Van den Heuvel-Eibrink et al., 2001); for example, an analysis in 405 AML patients of the three most frequent single nucleotide polymorphisms (SNPs) of the *MDR1* gene – C1236T, G2677T, and C3435T – demonstrated that although the C/C genotype of C3435T was associated with lower *MDR1* expression, it was also significantly associated with the highest probability of relapse, and poor OS (Illmer et al., 2002). Consistent with these findings, the C/C genotype of *MDR1* C3435T was associated with lower EFS and OS probability in pediatric ALL, although the T/T genotype was associated with risk of developing ALL (Jamroziak et al., 2004); similar findings were reported from an analysis of 147 Indian ALL patients (Rao et al., 2010) and a study of 105 Taiwanese pediatric ALL patients (Yang et al., 2010). In contrast, a study of 101 Asian AML patients showed that the C/C genotype of *MDR1* C3435T, although associated with lower P-gp expression in leukemic blasts versus the C/T and T/T genotypes, was associated with longer 3-year EFS, but not OS; in addition, the G/G genotype of G2677T was also associated with better 3-year EFS (Kim et al., 2006).

A number of studies have reported an absence of associations between genotype and response and/or outcome; for example, van der Holt et al reported no associations between any genotypes of C1236T, G2677T, or C3435T *MDR1* polymorphisms and P-gp expression and function in leukemic blasts, *MDR1* expression, CR rate, or survival in an analysis of 150 AML patients aged ≥60 years treated within a phase 3 study (van der Holt et al., 2006). Other studies have also

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reported no association between *MDR1* C3435T polymorphisms and P-gp function in leukemic blasts (Jamroziak et al., 2006; Hur et al., 2008; Jamroziak et al., 2005), or with response and long-term outcomes in AML patients (Hur et al., 2008; Jamroziak et al., 2005). In addition, the C/C genotype of C3435T was not associated with prognosis in a study of 143 Indian AML patients (Rao et al., 2010). Similarly, a single-center retrospective analysis of 262 AML patients did not identify any *MDR1* polymorphisms associated with survival (Hampras et al., 2010), and an analysis of 45 Turkish AML/ALL patients showed no significant effect of C3435T, G2677T and T-129C polymorphisms on P-gp-mediated drug resistance (Kaya et al., 2005). In contrast with studies described earlier, an analysis of 53 ALL patients identified no association between the C3435T *MDR1* polymorphism and ALL resistance or prognosis (Efferth et al., 2003).

Studies have also assessed the prognostic impact of *BCRP, MRP1* and other MDR gene polymorphisms in AML (Table 2). A single-center retrospective study identified a SNP in the *BCRP* gene that was associated with improved OS, compared with the wild-type genotype, as well as increased risk of toxicity (Hampras et al., 2010). In a study of 112 Israeli AML patients, *ABCC3* C-211T polymorphism and *GSTM1* null genotype were associated with poor prognosis (Muller et al., 2008). In contrast, an analysis of 111 AML/ALL patients showed that there were no significant associations between any of the genotypes of T2684C, C2007T, C2012T, and C2665T *MRP1* polymorphisms on *MRP1* expression and chemosensitivity, despite high *MRP1* expression being associated with MDR in both AML and ALL (Mahjoubi et al., 2008).

The effects of genetic variants in drug transporter genes associated with phenotypical consequences are still controversial, as contradictory results have been reported. Most published studies report experiences from small sample sizes in relation to the allele and genotype frequency of the studied variant, and results may have been affected by potentially confounding factors with respect to the patient population as well as the probe drug. Transporters interact with drug metabolism enzymes and are regulated with several nuclear receptors. Probe drugs are usually substrates for multiple transporters and metabolism enzymes. Thus, to evaluate the genetic component of drug transporter function, a more integrated approach, considering several genes involved in specific functional units and pathways, is necessary. Given the presence of linkage disequilibrium, which exists for many SNPs investigated to date, studies of the effects of haplotypes, rather than of SNPs, are

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increasing. Other factors such as lifestyle, concomitant medication, and comorbidities must also be considered in addition to a patient's genetic make-up.

Notable examples of the prognostic impact of MDR expression in other cancers

Expression and/or function of *MDR1* and other MDR genes have also been reported to be of prognostic relevance in multiple other cancers, including colorectal cancer (Balcerczak et al., 2010), esophageal squamous cell carcinoma (Yamasaki et al., 2011), gastric cancer (Zhang and Fan, 2010), chronic lymphoproliferative disorders (Drain et al., 2010), and breast cancer (Germano and O'Driscoll, 2009). Further, a prognostic impact of MDR gene polymorphisms has also reported in other cancers. For example, C1236T, G2677T, and C3435T *MDR1* polymorphisms, and the G/G genotype in BCRP (rs2231137), have been shown to affect resistance to imatinib in patients with chronic myeloid leukemia (CML) (Ni et al., 2011; Kim et al., 2009; Dulucq et al., 2008), while some polymorphisms in *MDR1* and *MRP1* were shown to have a prognostic impact on response rate, time to progression (TTP)/PFS, and OS in patients with relapsed multiple myeloma treated with bortezomib plus pegylated liposomal doxorubicin (Buda et al., 2010). A recent review of studies reporting outcomes in patients with solid tumors according to *MDR1* polymorphisms identified some associations with outcome following paclitaxel/carboplatin treatment in ovarian cancer patients, but inconsistent results in other tumor types (Hamidovic et al., 2010). Interestingly, *MDR1* polymorphisms were also shown to be associated with rates of toxicity with 5-fluorouracil and capecitabine-based therapy in patients with colorectal cancer (Gonzalez-Haba et al., 2010). Additionally, *MDR1* polymorphisms have been shown to be a possible prognostic factor in colorectal cancer (Balcerczak et al., 2010), and *MRP2* and *MRP5* polymorphisms have been associated with poorer response to therapy and OS in pancreatic cancer (Tanaka et al., 2011).

OVERCOMING MDR ARISING FROM DRUG EFFLUX TRANSPORT

P-gp and other MDR protein inhibitors

Over the past couple of decades, a large number of putative inhibitors of P-gp have been investigated in both preclinical and clinical studies. However, while preclinical investigations have validated the approach of P-gp inhibition, these inhibitors have generally met with little success clinically, likely due to the complexity of the MDR phenotype, as well as potency and specificity issues (Yang et al., 2008; Dantzig et al., 2003; Szakacs et al., 2006). The first generation of P-gp inhibitors, comprising

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currently available drugs found to have P-gp inhibitory properties, included verapamil (Belpomme et al., 2000; Pereira et al., 1994), quinine (Wattel et al., 1999; Solary et al., 2003), and cyclosporine (List et al., 2001; Becton et al., 2006). Some studies provided evidence of the feasibility and utility of P-gp inhibition with these compounds; for example, addition of quinine to mitoxantrone and cytarabine therapy in patients with high-risk myelodysplastic syndromes (MDS) resulted in improved OS in P-gp-positive patients (Wattel et al., 1999), while in patients with poor-risk AML, cyclosporine added to daunorubicin and cytarabine resulted in improved OS (List et al., 2001), and cyclosporine plus daunorubicin increased the CR rate in patients with AML (Li et al., 2009).

Based on these promising initial results, second-generation inhibitors were developed based upon the first-generation inhibitors, but designed to have an improved toxicity profile. For example, the non-immunosuppressive cyclosporine analog valspodar (PSC-833) was studied with standard agents in previously untreated AML (Baer et al., 2002; Kolitz et al., 2004; Kolitz et al., 2010), elderly patients with AML (van der Holt et al., 2005), relapsed/refractory AML (Greenberg et al., 2004), and relapsed/refractory pediatric acute leukemia (O'Brien et al., 2010); however, there was only limited evidence of benefit in terms of CR rate or OS. Similarly, biricodar (VX-710) showed limited success in phase 3 trials and was, like valspodar, discontinued (Goldman, 2003). A key reason why these agents were not successful was their pharmacokinetic interactions with chemotherapeutic drugs. These arose due to non-drug-transporter inhibition, as well as altered biotransformation and tissue distributions, resulting in reduced systemic clearance, reduced metabolism of the chemotherapy, and thus lowering of the maximal tolerated doses (MTD) (Goldman, 2003; Bates et al., 2004; Patel and Tannock, 2009; Pein et al., 2007).

To overcome these issues, third-generation P-gp inhibitors have been designed to be more selective for transporter inhibition, with high affinity for efflux transporters, and to have low systemic pharmacokinetic interactions (Yang et al., 2008; Globisch et al., 2006; Martin et al., 1999; Mistry et al., 2001; Fox and Bates, 2007). They are non-competitive inhibitors, inhibiting P-gp activity by binding to the transporter protein without themselves being substrates (Martin et al., 1999; Mistry et al., 2001; Di Nicolantonio et al., 2004; Shepard et al., 2003). Some of these newer agents are inhibitors of P-gp and/or other transporters (Gardner et al., 2009; Lagas et al., 2009), potentially extending the range of tumor types in which they may have beneficial

Molecular Pharmacology Fast Forward. Published on July 23, 2012 as DOI: 10.1124/mol.112.079129
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effects. Preclinical studies have demonstrated the effectiveness of these agents in reversing or overcoming MDR in leukemia cells. For example, zosuquidar restored drug sensitivity in P-gp-expressing leukemia cell lines and enhanced anthracycline cytotoxicity in P-gp-active primary AML blasts (Tang et al., 2008). Tariquidar has also been shown to be a highly effective P-gp inhibitor (Fox and Bates, 2007), increasing paclitaxel concentration in the brain (Hubensack et al., 2008), and reversing MDR in both *in vitro* and *in vivo* studies (Mistry et al., 2001). Similarly, the imidazole derivative FG020326 potentiated paclitaxel, doxorubicin, and vincristine activity in P-gp-overexpressing cell lines and enhanced paclitaxel and vincristine antitumor activity *in vivo* (Dai et al., 2009).

Unfortunately, the findings from clinical studies of these agents have not necessarily reflected the promising preclinical data, possibly due to multiple factors including the presence in patients of multiple mechanisms of MDR rather than just the specific target of these agents, the tolerability of MDR inhibitors, and the poor pharmacokinetics of MDR inhibitors. For example, despite having been shown to rapidly inhibit P-gp-mediated rhodamine-123 efflux in AML patient cells in a phase 1 study (Gerrard et al., 2004), addition of zosuquidar to standard cytarabine and daunorubicin induction therapy in a randomized study of patients aged >60 years with newly diagnosed AML or MDS did not result in improved outcomes (Cripe et al., 2010). In a phase 1 study of tariquidar in combination with vinorelbine, a modest reduction in the maximum tolerated dose of vinorelbine was seen, compared with the standard therapeutic dose (Abraham et al., 2009).

In addition, it may be argued that suboptimal study design could have contributed to the failure of these clinical studies of MDR inhibitors (van Zuylen et al., 2000). In particular, as noted earlier, although multiple assays have been developed and utilized for the evaluation of efflux pump activity, a definitive link between assay results and activity remains to be established for a specific assay and a specific MDR protein. Consequently, the anticipated effect size in clinical trials would be hard to predict. Furthermore, numerous trials did not make use of surrogate markers for MDR activity, and no patient selection criteria were applied, such as selecting only patients with P-gp-positive tumors.

Nevertheless, in spite of these potential mitigating factors with regards to the outcomes of the clinical trials, it appears that the strategy of efflux pump inhibition is no longer a favored approach for overcoming MDR. In the absence of potent,

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selective efflux pump inhibitors, together with associated validated assays, the development of efflux pump inhibitors appears to be declining due to multiple factors, including the complexity of the pharmacokinetics associated with these agents. Thus, this strategy may be confined to history, given the substantially greater interest in other ongoing approaches, including the development of novel compounds that are not efflux pump substrates, as discussed later.

Novel anti-cancer agents that inhibit MDR function and expression

Numerous other agents and approaches are being investigated with the aim of improving MDR inhibition. For example, multiple novel targeted anti-cancer agents have been shown to have inhibitory properties against P-gp and other MDR protein activity, either through direct inhibition, through acting as a competitive transporter substrate, or as a consequence of downstream signaling effects resulting from target inhibition.

A number of farnesyltransferase and tyrosine kinase inhibitors have demonstrated the ability to reverse MDR. Tipifarnib significantly inhibited daunorubicin efflux in leukemia cell lines overexpressing P-gp and showed synergistic proliferation inhibition and apoptosis induction (Medeiros et al., 2007), while lapatinib, erlotinib, and nilotinib have also been shown to inhibit the efflux activity of P-gp and BCRP through being substrates for these transporters (Dai et al., 2008; Shi et al., 2007; Shi et al., 2009; Dohse et al., 2010). Additionally, BIBF 1120, an inhibitor of vascular endothelial growth factor receptors, platelet-derived growth factor receptors, and fibroblast growth factor receptor tyrosine kinases, inhibited P-gp activity in P-gp-overexpressing cancer cells, and enhanced doxorubicin and paclitaxel cytotoxicity (Xiang et al., 2011). A number of studies have also suggested the utility of phosphodiesterase-5 inhibitors as inhibitors of MDR protein-mediated efflux through their roles as substrates of these pumps. For example, sildenafil has been shown to inhibit the transporter functions of P-gp and BCRP and to stimulate their ATPase activity, and thus to sensitize MDR cells to chemotherapeutic drugs (Shi et al., 2011b; Shi et al., 2011a). Similarly, vardenafil was shown to block the drug-efflux role of P-gp and to stimulate its ATPase activity in a MDR human epidermoid carcinoma cell line (Ding et al., 2011), indicating that it is a transport substrate of P-gp. The evidence is less consistent for the utility of histone deacetylase inhibitors (HDACs) for overcoming MDR. HDACs have recently been shown to downregulate MRP2 protein expression, but not MDR1 and BCRP expression, in the MDR KBV20C cell line (Kim et al., 2011), an effect possibly mediated by HDAC inhibitor-induced expression of IL-

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6-type cytokine receptors (Blanchard et al., 2002) such as for oncostatin M (Le Vee et al., 2011). Conversely, other recent studies of HDACs in AML cells showed that these agents, including suberoylanilide hydroxamic acid and valproate, in combination with various chemotherapy agents, induced the activity of *MDR1*, BCRP, MRP7, and MRP8, and thus resulted in reduced apoptosis and resistance (Hauswald et al., 2009).

A number of studies have shown that targeted agents inhibiting specific pathways may induce downstream effects on MDR as a consequence of signalling inhibition. For example, the doxorubicin-induced overexpression of *MDR1* in HL-60 AML cells has been suggested to be regulated by the cyclo-oxygenase (COX) system, particularly COX-2, indicating a potential role for COX-2 inhibitors in ameliorating induced resistance (Puhlmann et al., 2005). Indeed, in a recent report, the COX-2 inhibitor SC236, as well as the non-steroidal anti-inflammatory drug indomethacin, were shown to inhibit P-gp and MRP1 expression and thus enhanced doxorubicin cytotoxicity in a MDR hepatocellular carcinoma cell line (Ye et al., 2011). Another potential therapeutic target in MDR leukemia may be STAT3 signaling; a recent study showed that STAT3 was overexpressed in K562/AO2 leukemia MDR cells, and inhibition of STAT3 activation resulted in downregulation of *MDR1* transcription and P-gp expression (Zhang et al., 2011c).

Multiple other recent cell-line studies have demonstrated that numerous novel compounds have the ability to inhibit MDR function, although no clinical studies have been reported. For example, curcumin has been shown to have inhibitory activity against *MDR1* expression in patient leukemic cells (Anuchapreeda et al., 2006) and the combretastatin A-4 analog MZ3 overcame MDR in leukemia cells by downregulating *MDR1* transcription and anti-apoptotic protein expression (Xu et al., 2008). Additionally, two milbemycin compounds (Gao et al., 2011), two novel acrylonitrile derivatives (Yamazaki et al., 2011), and a number of benzo(a)quinolizin-4-ones (Kanintronkul et al., 2011) showed chemosensitizing properties due to modulation of P-gp, while X-shaped poly(ethylene oxide)-poly(propylene oxide) block copolymers (poloxamines) inhibited P-gp and BCRP in hepatic carcinoma cell lines (Cuestas et al., 2011). A number of flavonoid compounds from various plant species have recently been shown to inhibit the function of BCRP (Versiani et al., 2011) and to inhibit vinblastine-stimulated but promote daunorubicin-stimulated P-gp activity in leukemic T-cells (Tran et al., 2011), and limonin and other citrus compounds enhanced doxorubicin cytotoxicity in CEM/ADR5000 MDR leukemia cells (El-Readi

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et al., 2010). Finally, use of an ATP analog that was shown to interact with the drug- and ATP-binding sites of P-gp resulted in reduced P-gp efflux activity (Ohnuma et al., 2011).

Non-chemical MDR inhibition

Multiple additional approaches to MDR inhibition have been investigated (Figure 1). For example, small interfering RNA (siRNA), including short hairpin RNA (shRNA), targeted at MDR genes has been shown to be effective in a number of studies (Wu et al., 2008). shRNA/siRNA targeting *MDR1* was shown to be effective at inhibiting P-gp expression and resensitizing cells to harringtonine and curcumin when transfected into MDR HT9 leukemia cells (Shao et al., 2010), and to downregulate P-gp expression and increase drug sensitivity in MDR K562/Adr leukemia cells (Lim et al., 2007). Additionally, a combination of daunorubicin-conjugated magnetic Fe_3O_4 nanoparticles and shRNA expression vector aimed at *MDR1* mRNA overcame resistance in K562/AO2 MDR leukemia cells (Chen et al., 2010), while a potential interaction between the glucosylceramide synthase (GCS) gene and *MDR1* was shown by GCS siRNA resulting in not only GCS mRNA but also *MDR1* mRNA downregulation in K562/AO2 cells (Zhang et al., 2011d); this relationship is reinforced by studies showing that chemosensitization with the GCS inhibitor Genz-123346 is mediated through P-gp inhibition (Chai et al., 2011).

Alternative approaches to gene silencing, including the use of antisense oligonucleotides (Kang et al., 2004), transcriptional regulation (Xu et al., 2002), and targeted ribozymes (Kowalski et al., 2002), have also been studied (Wu et al., 2008). P-gp downregulation mediated by RNAi gene silencing has been demonstrated to be effective (Abbasi et al., 2011a; Abbasi et al., 2011b), with antisense oligonucleotide against *MDR1* mRNA resulting in decreased P-gp and mRNA expression, indicating reversal of the MDR phenotype, in leukemic cells (Nadali et al., 2007). In a novel approach to overcoming MDR, xanthones have been studied in MRP1-overexpressing cells and shown to induce apoptosis through activation of MRP1-mediated glutathione efflux, an effect that was not seen in non-MDR cells (Genoux-Bastide et al., 2011). This property of ‘collateral sensitivity’ (Hall et al., 2009) has also been reported with the first-generation P-gp inhibitor verapamil (Trompier et al., 2004) and the propanoylglycine derivative tiopronin (Goldsborough et al., 2011).

New agents with reduced drug efflux properties

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As an alternative approach to inhibiting the activity of P-gp and other drug efflux pumps, new therapeutic agents can be designed to avoid these efflux mechanisms and thus achieve high concentrations in cancer cells, potentially resulting in enhanced cell death. For example, existing chemotherapy agents may be modified so that they are no longer substrates for P-gp or other MDR proteins, and thus evade the efflux mechanism (Nobili et al., 2011). One example of a new therapeutic agent that has reduced drug efflux properties is amonafide, a novel topoisomerase II inhibitor. While topoisomerase II inhibitors daunorubicin, doxorubicin, idarubicin and others are substrates of P-gp, which causes their rapid efflux from leukemia cells, amonafide has been shown to be neither a substrate nor an inhibitor of P-gp (Chau et al., 2008). Consequently, amonafide has been suggested as a potential agent for the treatment of AML (Allen and Lundberg, 2011). Similarly, the recently approved taxane cabazitaxel, a dimethyloxy derivative of docetaxel, has no affinity for P-gp and can cross the blood-brain barrier, unlike docetaxel and paclitaxel (Paller and Antonarakis, 2011). Other novel agents that have been shown not to be substrates of P-gp or other efflux pumps include the glutathione S-transferase (GST) inhibitor NBDHEX (Ascione et al., 2009) and a series of pyrrolo-1,5-benzoxazepine compounds (Nathwani et al., 2010).

Alternatively, agents may be designed to be more lipophilic and thus more readily influxed; similarly, encapsulation of agents in liposomes may help overcome MDR, as reported with pegylated liposomal doxorubicin (Riganti et al., 2011) and stealthy liposomal encapsulation of vincristine and quinacrine (Liang et al., 2008). These approaches, which increase the passive lipid permeability of compounds and result in improved passive diffusion, preventing the development of large concentration gradients, may potentially alleviate resistance due to efflux transporters irrespective of whether a compound is a substrate or not (Raub, 2006). This concept may be demonstrated, albeit in reverse, through related work on uptake transporters and imatinib, the ‘gold standard’ for treatment of CML, and the second-generation agent nilotinib. Both agents are substrates for MDR efflux transporters as well as various solute carrier family transporters, including the hOCT1 (human organic cationic transporter 1) influx protein (Minematsu and Giacomini, 2011); however, nilotinib is more hydrophobic than imatinib and enters cells more rapidly. Thus, while imatinib uptake is decreased when hOCT1 activity is low (White et al., 2006; Crossman et al., 2005), resulting in poorer response in CML patients (Engler et al., 2011; White et al., 2007), nilotinib uptake is unaffected by hOCT1 activity level (Davies et al., 2009; White et al., 2006).

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Influx and efflux kinetics of doxorubicin were shown to be altered to enhance cytotoxicity in K562 KD30 MDR leukemia cells through the linking of doxorubicin with a hybrid cell-penetrating and drug-binding peptide (Zheng et al., 2010). Similarly, nanotechnology has been shown to be a promising approach to help therapeutic agents evade efflux. Doxorubicin attached to 2–8 nM nanodiamond carriers has been shown to increase apoptosis compared with free doxorubicin in MDR liver cancer both *in vitro* and *in vivo* (Merkel and DeSimone, 2011), while anti-P-gp antibody functionalized single-walled carbon nanotubes loaded with doxorubicin demonstrated enhanced cytotoxicity towards K562R MDR leukemia cells versus free doxorubicin, thus overcoming the resistance of these cells (Li et al., 2010). Additionally, multifunctional nano-assemblies carrying vincristine sulfate resulted in higher levels of vincristine uptake in P-gp-overexpressing cells, overcoming efflux and vincristine MDR (Zhang et al., 2011b), while nanoparticle-mediated delivery of paclitaxel and tariquidar demonstrated significantly enhanced cytotoxicity in drug-resistant tumor cells (Patil et al., 2009).

PERSPECTIVES ON FUTURE DIRECTIONS

This review has highlighted the importance of MDR in cancer and particularly in acute leukemia. Given the potential impact of MDR on the efficacy of anticancer therapeutics, this is clearly a key issue to be considered during the development of novel therapeutic agents. As described above, there is a substantial body of research into P-gp inhibition as a means of improving the efficacy of therapeutic agents that are ABC transporter substrates, and there are a large number of potential inhibitors in development. For successful MDR modulation in acute leukemia, particularly AML, these inhibitors must be specific to the ABC transporters known to be associated with a patient's MDR, for example targeting both P-gp and BCRP, in order to avoid adverse effects arising from off-target inhibitory properties. However, even with targeted inhibition of the key mediators of MDR, due to the complexity of MDR in AML and other cancers, it is likely that inhibition may not necessarily provide a feasible therapeutic approach, as suggested by the results of clinical trials with the third-generation agents. Thus, the alternative approach of developing novel agents with reduced efflux properties may prove to be the most promising way of improving upon the efficacy of existing agents for AML. Exploitation of the available resources and tools for identifying novel compounds that are toxic to MDR cancer cell lines and not substrates of P-gp or other transporters (Szakacs et al., 2004) will hopefully lead

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to the future development of novel therapeutic agents for acute leukemia and other cancers that will help overcome the established adverse prognostic impact of MDR in these diseases.

Molecular Pharmacology Fast Forward. Published on July 23, 2012 as DOI: 10.1124/mol.112.079129
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ACKNOWLEDGMENTS

The authors would like to acknowledge the writing assistance of Steve Hill of FireKite during the development of this publication, which was funded by Millennium Pharmaceuticals, Inc.

AUTHORSHIP CONTRIBUTION

Wrote or contributed to the writing of the manuscript: C.Q. Xia and P.G. Smith

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Molecular Pharmacology Fast Forward. Published on July 23, 2012 as DOI: 10.1124/mol.112.079129
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FOOTNOTES

This work was supported by Millennium Pharmaceuticals, Inc.

Disclosures of conflicts of interest

CQX is, and PGS was, an employee of Millennium Pharmaceuticals, Inc. (Since the development of this manuscript, PGS has left Millennium Pharmaceuticals, Inc.)

Molecular Pharmacology Fast Forward. Published on July 23, 2012 as DOI: 10.1124/mol.112.079129
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LEGEND FOR FIGURE

Figure 1. Overcoming MDR – current approaches to eliminating drug resistance through efflux

TABLES

Table 1. ABC transporters involved in anti-cancer drug resistance (Moitra et al., 2011; Dean et al., 2001; Szakacs et al., 2006)

Gene	Protein	Role(s) in drug resistance	Anticancer drug substrates/inducers
ABCA2	ABC2	Drug transport	Estramustine, mitoxantrone
ABCA3	ABC3	Surfactant lipid transporter, lysosomal drug sequestration (Chapuy et al., 2008)	Doxorubicin, daunorubicin (Steinbach et al., 2006), imatinib (Chapuy et al., 2009)
ABCB1	P-gp / MDR1	Drug transport	Multiple, including vinca alkaloids, anthracyclines, etoposide, taxanes, imatinib, irinotecan, methotrexate, mitoxantrone
ABCB4	PGY3 / MDR3	Phosphotidyl choline and drug transport, bile acid secretion	Vinblastine (Wang et al., 2008), doxorubicin (Turton et al., 2001)
ABCB5	ABC19	Drug transport	Fluorouracil (Wilson et al., 2011), doxorubicin (Frank et al., 2005)
ABCB11	SPGP	Bile salt transport, drug transport	Paclitaxel
ABCC1	MRP1	Drug transport	Multiple, including vinca alkaloids, anthracyclines, etoposide, imatinib, irinotecan, methotrexate, mitoxantrone
ABCC2	MRP2	Organic anion efflux, drug transport	Multiple, including vinca alkaloids, anthracyclines, etoposide, taxanes, irinotecan, cisplatin, methotrexate, mitoxantrone
ABCC3	MRP3	Drug transport	Etoposide
ABCC4	MRP4	Nucleoside transport, drug transport	Irinotecan, thiopurines, methotrexate
ABCC5	MRP5	Nucleoside transport, drug transport	Thiopurines, cisplatin, methotrexate
ABCC6	MRP6	Drug transport	Anthracyclines, etoposide, cisplatin, gemcitabine (Ikeda et al., 2011)
ABCC10	MRP7	Drug transport	Vinca alkaloids, taxanes

ABCC11	MRP8	Drug transport	5-fluorouracil
ABCC12	MRP9	Drug transport	None identified
ABCG2	ABCP / BCRP1	Toxin efflux, drug transport	Multiple, including anthracyclines, etoposide, imatinib, flavopiridol, irinotecan, methotrexate, mitoxantrone
LRP	LRP	Major vault transporter protein (Scheffer et al., 1995)	AML induction chemotherapy (Huh et al., 2006; List et al., 1996)

Table 2. MDR gene polymorphisms and associations with clinical outcome in acute leukemia and other cancers.

MDR gene	Polymorphism	Genotype	Cancer type	Association with clinical outcome
MDR1	C1236T	–	Untreated AML	None reported (Illmer et al., 2002; Hampras et al., 2010)
		–	Untreated AML, aged ≥60 years	No association with CR rate or survival reported (van der Holt et al., 2006)
		TT vs CT vs CC	CML	Higher rate of major molecular response to imatinib (85% vs 53% vs 41%, p=0.008) (Dulucq et al., 2008)
		TT vs CT/CC	CML	Higher rate of resistance to imatinib (75% vs 31%, p=0.004) (Ni et al., 2011)
		TT vs CT/CC	Colorectal cancer	Decreased risk of death (HR 0.26, p=0.0424) (Balcerczak et al., 2010)
	G2677T	GG/TT vs GT	Relapsed/refractory AML	Shorter relapse-free interval (p=0.002) and poorer survival rate (p=0.02) (Van den Heuvel-Eibrink et al., 2001)
		GG vs GT/TT	Untreated AML	Higher probability of CR (p=0.04), higher 3-year EFS rate (61% vs 22%, p=0.0241), no OS difference (Kim et al., 2006)
		–	Untreated AML	None reported (Illmer et al., 2002; Hampras et al., 2010; Kaya et al., 2005)
		–	Untreated AML, aged ≥60 years	No association with CR rate or survival reported (van der Holt et al., 2006)
		GG	Pediatric ALL	Reduced EFS (HR 6.8, p=0.01) (Yang et al., 2010)

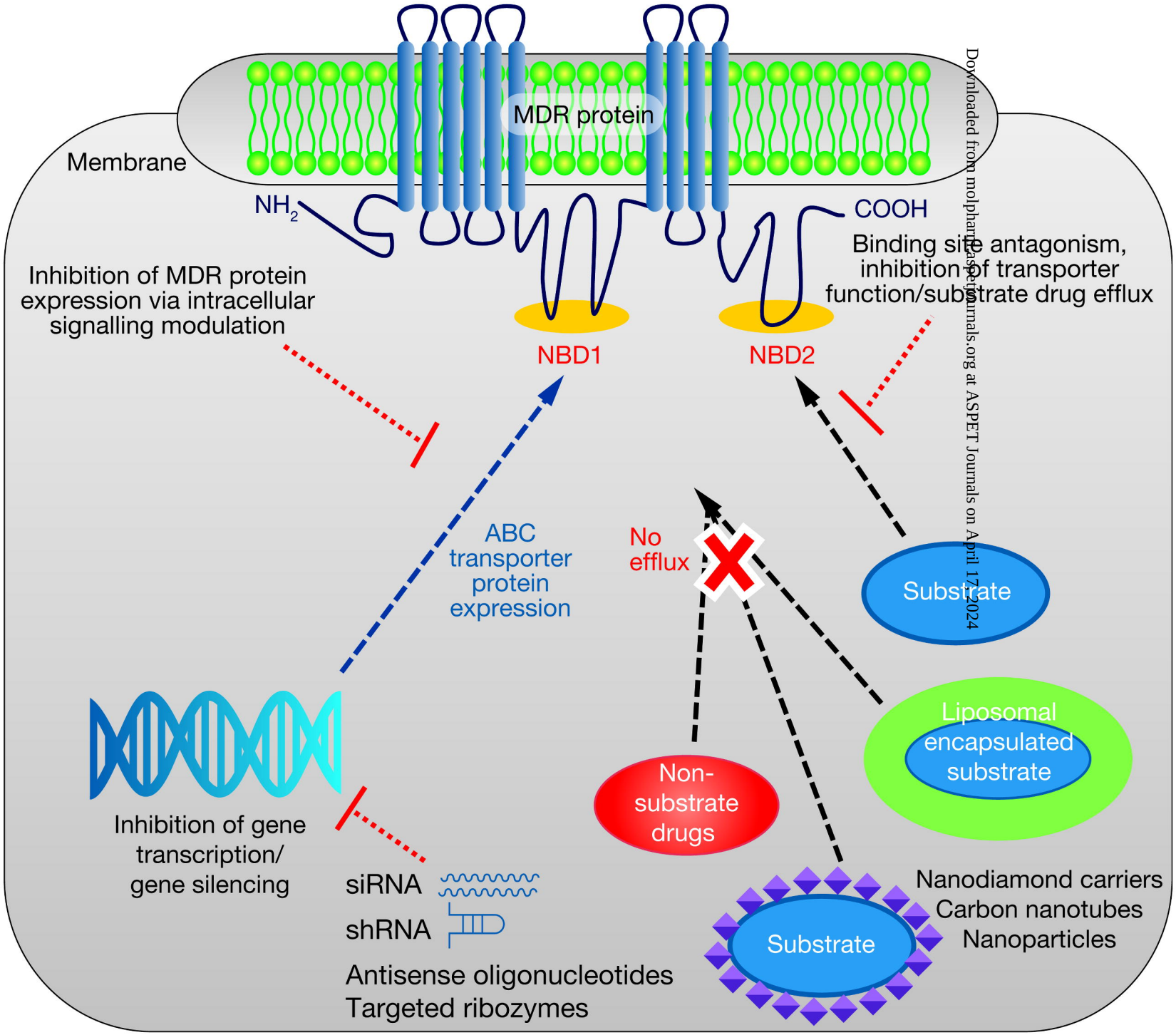
G2677T/A	AG/AT/AA vs TT/GT/GG	CML	Higher rate of complete cytogenetic remission with imatinib (p=0.02) (Ni et al., 2011)
	TT/TA vs GG/GT/GA	CML	Higher rate of major molecular response with imatinib (OR 3.94, p=0.018) (Dulucq et al., 2008)
C3435T	CC/CT vs TT	Untreated, intermediate-risk AML	Increased probability of relapse (84% vs 45%, p=0.02; multivariate analysis RR 2.4, p=0.02); lower OS rate (14% vs 37%, p=0.1; multivariate analysis RR 2.1, p=0.02) (Monzo et al., 2006)
	CC vs CT/TT	Untreated AML	Increased risk of relapse (p<0.001) and poorer OS (p<0.01) (Illmer et al., 2002)
	CC vs CT/TT	Untreated AML	Higher probability of CR (p=0.05), higher EFS (p=0.0139), no OS difference (Kim et al., 2006)
	–	Untreated AML, aged ≥60 years	No association with CR rate or survival reported (van der Holt et al., 2006)
	–	Untreated AML	None reported (Illmer et al., 2002; Rao et al., 2010; Hur et al., 2008; Jamroziak et al., 2005; Hampras et al., 2010; Kaya et al., 2005)
	CC vs CT/TT	Pediatric ALL	Lower EFS probability (62% vs 87%, p=0.007; HR 3.9, p=0.008) and OS probability (72% vs 91%, p=0.006; HR 3.3, p=0.02) (Jamroziak et al., 2004)
	CC	Pediatric ALL	Reduced EFS (HR 21.7, p=0.009) (Yang et al., 2010)

		–	Adult ALL	None reported (Jamroziak et al., 2005)
		CC vs CT/TT	CML	Lower rate of resistance to imatinib (25% vs 59%, p=0.023) (Ni et al., 2011)
	rs1045642	CC/CT vs TT	CML	Better OS following imatinib (HR 3.70, p=0.04) (Kim et al., 2009)
		TT vs CC vs CT	MM	Better PFS (p=0.0578), response rate (p=0.0782), and TTP (p=0.0601) in patients treated with bortezomib plus pegylated liposomal doxorubicin (Buda et al., 2010)
BCRP/ ABCG2	G34A	AG/AA vs GG	Untreated AML	Improved OS (HR 0.44, 95% CI: 0.25, 0.79) (Hampras et al., 2010)
	rs2231137	GG vs AG/AA	CML	Adverse impact on achievement of a major cytogenetic response (HR 0.68, p=0.05) or a complete cytogenetic response (HR 0.63, p=0.02) to imatinib (Kim et al., 2009)
	rs2231142	AA vs AC/CC	CML	Adverse impact on achievement of a major molecular response (HR 0.40, p=0.004) or a complete molecular response (HR 0.42, p=0.006) to imatinib (Kim et al., 2009)
ABCC3	C-211T	–	Untreated AML	Adverse prognostic significance (treatment response and survival) (Muller et al., 2008)
GSTM	null alleles		Untreated AML	Adverse prognostic significance (treatment response and survival) (Muller et al., 2008)
MRP1	T2684C, C2007T, C2012T, C2665T	–	AML/ALL	No impact on response to therapy (Mahjoubi et al., 2008)

	R723Q	GG vs AG	MM	Improved TTP (p=0.0008), PFS (p=0.0006), and OS (p=0.0045) in patients treated with bortezomib plus pegylated liposomal doxorubicin (Buda et al., 2010)
MRP2	G40A	GG	Pancreatic cancer	Poor histologic response to chemoradiotherapy (p=0.028) and reduced OS (p=0.097) (Tanaka et al., 2011)
MRP5	A-2G	AA	Pancreatic cancer	Poor OS (HR 1.65, p=0.01) (Tanaka et al., 2011)

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; EFS, event-free survival; MM, multiple myeloma; OS, overall survival; PFS, progression-free survival; RR, relative risk; TTP, time to progress

Figure 1



NBD, nucleotide binding domain