The Reciprocal Interaction of Small Molecule Protein Kinase Inhibitors and ATP-Binding Cassette Transporters in Targeted Cancer Therapy

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Abstract: Protein kinases have become the second most important group of drug targets, after G-protein-coupled receptors. Currently, 15 small molecule protein kinase inhibitors (PKIs) have received food and drug administrator (FDA) approval to be used as cancer treatments. However, in the course of clinical use of these small molecule PKIs, drug resistance has become a recurring problem. Their therapeutic potential depends on access to their intracellular targets, which significantly affected by certain membrane ATP-binding cassette (ABC) transporters. ABC transporters were major causes of clinical multiple drug resistance (MDR) and might be resulting in the development of resistance to PKIs in cancer patients. Some PKIs could modulate the activity of ABC transporters and affect the metabolism of themselves and other chemically unrelated drugs. Moreover, it has been recently reported that some PKIs could regulate the expression of ABC transporters in tumor cells, thereby affect their intracellular accumulation and antitumor efficacy. In this review, the reciprocal interaction of clinically important PKIs with the MDR-related ABC transporters, in particular ABCB1 and ABCG2, was summarized.

Keyword: Protein Kinase Inhibitors, ABC Transporters, P-gp/ABCB1, BCRP/ABCG2, Targeted Cancer Therapy.

1. INTRODUCTION

The development of novel cancer medicines has shifted from conventional cytotoxic drugs to targeted therapies, which modulate molecules with activities relevant to a given oncogenic phenotype [1]. The molecular targeted agents promise to be a more effective form of anticancer therapy with fewer side effects [2]. Protein kinases have emerged as the most important class of targets in oncology drug discovery because of their major roles in regulating cell growth and survival [3]. Protein kinase inhibitors (PKIs) are highly promising agents for specific inhibition of malignant cell growth and metastasis. However, their therapeutic potential is also limited by multidrug resistance (MDR) mediated by ATP-binding cassette (ABC) transporters in cell lines, and potentially important in the clinical setting.

Recently, ABC transporters were found to be associated with cellular resistance to PKIs [4-8]. It has been described that several PKIs are able to interact with members of the ABC family of transporters such as P-glycoprotein (P-gp/ABCB1), multidrug resistance-associated protein 1 (MRP1/ABCC1), and breast cancer resistance protein (BCRP/ABCG2) [5, 7, 9, 10]. Some PKIs are substrates or inhibitors of the drug transporters P-gp/ABCB1and BCRP/ABCG2 [11, 12]. A better understanding of the substrates or inhibitors of the MDR-ABC transporters has important implications in development of novel PKI drugs for treatment of cancer. In this review, we detailed the information of various PKIs approved by FDA, and summarized the recent studies regarding the reciprocal interaction of these PKIs and ABC transporters.

2. PKIS AS ANTI-CANCER AGENTS

Protein kinases play a key role in regulating signal transduction and cell cycle pathways. Selective inhibition of protein kinases is a well accepted therapeutic approach for treatment of various diseases [13, 14]. More than 500 human genes encode proteins that serve as kinases. And 478 of these belong to a single group whose catalytic domains are related in sequence and are classified into a number of subsets or families based mainly on sequence and structure similarities [15-17]. Four groups of protein kinases are commonly described. The first group comprises the

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receptor tyrosine kinases including epidermal growth factor receptor (EGFR), insulin-like growth factor-1 receptor (IGF-1), vascular endothelial growth factor receptor (VEGFR), fibroblast growth factor receptor (FGFR) 1, 3, and 4, FMS-like tyrosine kinase (FLT) and Mast/stem cell growth factor receptor (SCFR; c-KIT) [18]. The second group comprises the non-receptor tyrosine kinases such as c-SRC, ABL1, Janus kinase 2 (JAK2), c-YES, and focal adhesion kinase [13, 18, 19]. The third group comprises the lipid kinases, including phosphatidylinositol 3-kinase (PI3K). A key downstream effector of PI3K is the serine-threonine kinase AKT, and the PI3K/AKT pathway is known to play an important role in cell growth and survival [20]. The fourth group comprises the serine/threonine kinases, which include proteins such as AKT, ataxia telangiectasia mutated, mammalian target of rapamycin, S6 kinase, b-RAF and the cell cycle control kinases such as cyclin-dependent kinases, aurora kinases, and polo-like kinases [18].

The protein kinases have become prime targets for drug intervention in the diseased state, especially in cancer. Deregulation of protein kinase activity is known to be an important factor in tumorigenesis, and this finding has accelerated the development of a number of novel anti-cancer agents that target this family of proteins [13]. This crucial role has also made protein kinases an extremely important and tractable therapeutic class for oncology drug discovery and became the second-largest drug target family, with 15 approved small molecule PKI drugs (Table **1**) and many more compounds in clinical trials as well as in preclinical development for treatment of cancer [18, 21-23].

Most of protein kinase inhibitors are ATP-competitive and are called type I inhibitors. The ATP-binding pocket is highly conserved among members of the kinase family and it is difficult to find selective agents. The non-ATP competitive inhibitors, called type II and type III inhibitors, offer the possibility to overcome these problems. These inhibitors act by inducing a conformational shift in the target enzyme such that the kinase is no longer able to function. In the DFG-out form, the phenylalanine side chain moves to a new position. This movement creates a hydrophobic pocket available for occupation by the inhibitor. Some common features are present in these inhibitors. They contain a heterocyclic system that forms one or two hydrogen bonds with the kinase hinge residue. They also contain a hydrophobic moiety that occupies the pocket formed by the shift of phenylalanine from the DFG motif. Moreover, all the inhibitors bear a hydrogen bond donor-acceptor pair, usually urea or amide, which links the hinge-binding portion to the hydrophobic moiety and interacts with the allosteric site. Some of these are allosteric inhibitors that alter kinase

Table 1: Fifteen PKIs Approved by FDA Until 2012

No	Name	Clinical Applications	FDA Approved Date
1	Imatinib	ALL, CEL, HES, CML, DFSP, GIST, MDS/MPD, SM	May 10, 2001
2	Nilotinib	CML	Oct 29, 2007
3	Bosutinib	CML	Sep 4, 2012
4	Gefitinib	NSCLC	Jun 17, 2005
5	Pazopanib	RCC, Soft tissue sarcoma	Oct 19, 2009
6	Vandetanib	Medullary thyroid cancer	Apr 6, 2011
7	Axitinib	RCC	Jan 27, 2012
8	Erlotinib	NSCLC, Pancreatic cancer	Nov 18, 2004
9	Lapatinib	Breast cancer	Mar 13, 2007
10	Sorafenib	Hepatocellular carcinoma, RCC	Dec 20, 2005
11	Sunitinib	GIST, Pancreatic cancer, RCC	Jan 26, 2006
12	Dasatinib	ALL, CML	Jun 28, 2006
13	Crizotinib	NSCLC	Aug 26, 2011
14	Vemurafenib	Melanoma	Aug 17, 2011
15	Ruxolitinib	Myelofibrosis	Nov 16, 2011

CEL, chronic eosinophilic leukemia; DFSP, dermatofibrosarcoma protuberams; MDS/MPD, myelodysplastic/myeloproliferative disorders; SM, systemic mastocytosis.

conformation and prevent protein substrate binding. Other inhibitors directly compete with protein substrate binding [24].

3. MDR AND ABC TRANSPORTERS

MDR is a phenomenon that occurs when cancer cells develop resistance to a variety of anticancer drugs that are structurally and mechanistically unrelated, presenting a major obstacle to successful chemotherapy treatment [25, 26]. Changes in cellular drug accumulation caused by over-expression of multi-specific ABC transporters are widely regarded as the main molecular mechanism of MDR [27]. To date, it is known that about 13~14 out of 49 members of the ABC protein family are associated with MDR in cancer cells [28]. The vast majority of clinically important cases of MDR seem to be the result of over-expression of three ABC transporter proteins: P-gp/ABCB1, MRP1/ABCC1, and BCRP/ABCG2 [29]. These transporters use energy of ATP hydrolysis to pump anticancer drugs out of the cell and reducing their intracellular concentration and enabling cancer cells to survive [30].

P-gp/ABCB1, discovered in 1976, is one of the best characterized ABC transporters [31]. It is composed of two homologous halves, each containing a NBD and a TMD, and transports exogenous and endogenous amphipathic substrates out of cells using energy from ATP [32]. It is believed to play an important role in cellular detoxification by influencing the absorption and tissue penetration of xenobiotics [33]. P-gp /ABCB1 is highly expressed in leukemia, breast, ovarian, colon, kidney, adrenocortical, and hepatocellular cancers and its overexpression is inversely correlated with poor clinical prognosis [34]. P-gp/ABCB1 pumps out many structurally unrelated anti-cancer drugs, such as vinca alkaloids, anthracyclines and taxanes, suggesting the flexible nature of the substrate binding site of P-gp/ABCB1 [27]. A large number of studies have suggested that P-gp/ABCB1 is also a transporter that effluxes molecular targeted drugs such as PKIs.

MRP1/ABCC1 was first identified in 1992 in doxorubicin-resistant lung cancer cells [35]. MRP1/ABCC1 confers resistance to many anticancer drugs, antivirals, antibiotics, and other compounds [36]. MRP1/ABCC1 is expressed mainly in the basolateral membrane of polarized cell layers and its function in non-malignant cells is likely to be the participation in the final steps of cellular detoxification. Substrates predominantly transported by MRP1/ABCC1 are glutathione, glucuronate and sulfate conjugates of organic anions of exogenous and endogenous origin, as well as oxidized glutathione [37]. The protein also have some functions in certain aspects of the immune response, as LTC4, a glutathione conjugate, is a substrate that has high affinity for MRP1/ABCC1 [38].

BCRP/ABCG2, also named mitoxantrone resistance-associated protein (MXR), breast cancer resistance protein (BCRP) or placenta-specific ATP binding cassette transporter (ABCP), was first cloned from drug selected human breast cancer cells MCF-7 in 1998 [39]. BCRP/ABCG2 is a half transporter which contains one TMD and one NBD, and is therefore thought to homodimerize or heterodimerize to form the functional unit [39]. Similar to the MDR family of transporters in yeast, the location of the TMD and NBD is reversed in BCRP/ABCG2 compared to P-gp/ABCB1 [40]. Similar to P-gp/ABCB1, BCRP/ABCG2 is localized to the apical membrane in epithelial cells and normally expressed in organs such as the placenta, brain, liver, prostate, and intestine [41]. BCRP/ABCG2 is also detected in hematopoietic and other stem cells, suggesting that it may play an important role in the protective function of pluripotent stem cells [42]. Over-expression of BCRP/ABCG2 renders cancer cells resistant to many anti-cancer drugs including mitoxantrone, topotecan, methotrexate and some novel targeted therapeutic agents such as imatinib. It is also associated with poor response to chemotherapy in leukemia and breast cancer patients [43, 44].

Inhibition of ABC transporter-mediated drug efflux may re-sensitize MDR cancer cells to an effective MDR cancer treatment with chemotherapeutic agents. Currently, three generations of P-gp/ABCB1 inhibitors and a number of MRP1/ABCC1 and BCRP/ABCG2 inhibitors have been developed to enhance the effect of chemotherapeutic drugs on MDR cancer cells *in vitro* and *in vivo* [45, 46]. Inhibition of BCRP/ABCG2 and P-gp/ABCB1 could occur in other tissues including the blood-brain barrier (BBB) and the gut in cancer patients, which crucial for the pharmacokinetic profile of these drugs [44].

4. INTERACTION OF PKIS WITH ABC TRANSPORTERS

The most critical challenge for PKI therapeutics is the development of drug-resistance though various intrinsic and extrinsic cellular mechanism. In particular, some PKIs had been reported to be substrates and transported by ABC transporters, resulting in altered pharmacokinetics or development of resistance to

these drugs in cancer patients [6, 23]. Furthermore, some reports have highlighted that some PKIs could modulate the activity and expression of ABC transporters. Given that most of PKIs are type I inhibitors and competitively inhibit the access of ATP to the binding pocket on protein kinases. The competitive binding of these PKIs to the ATP-binding sites of ABC transporters could also inhibit the functions of these transporters and reverse the MDR of cancer cells. Thus, PKIs might work as dual modulators of ABC transporters such as P-gp/ABCB1 and BCRP/ABCG2 and modulate overall drug metabolism, including the fate of diverse, chemically or target-wise unrelated drugs [5, 47]. In this review, we will summarize here the reciprocal interaction between 15 FDA approved clinically important PKIs and ABC transporters, in particular P-gp/ABCB1 and BCRP/ABCG2.

4.1. BCR-ABL Tyrosine Kinase Inhibitor (TKI)

4.1.1. Imatinib

Imatinib was the first target-based tyrosine kinase small molecule inhibitor approved by FDA in 2001. It is a multi-targeted agent that inhibits ABL, ARG, KIT, FMS, platelet-derived growth factors (PDGFR), EGFR and DDR1 in an ATP competitive manner. It is indicated for the treatment of chronic myelogenous leukemia (CML), acute lymphoblastic leukemia (ALL), gastrointestinal stromal tumors (GISTs) and hypereosinophilic syndrome (HES) [23, 48]. The majority of patients with chronic-phase CML treated with imatinib maintain durable responses. However, relapse can occur after drug withdrawal and drug resistance is observed in a subset of patients. According to the long-term follow-up studies, imatinib is unable to eradicate the complete BCR-ABL expressing leukemic stem cell population, and resistance develops in many cases. Because CML is considered a stem cell disease, it is intriguing to postulate that inherent protective mechanisms such as the expression of ATP-binding cassette (ABC) transporters could contribute to relapse [49, 50].

Imatinib could interact with both P-gp/ABCB1 and BCRP/ABCG2 transporters. Several studies confirmed imatinib as a P-gp/ABCB1 substrate in various cell model systems [49, 51-53]. On the contrary, imatinib was also found to act as an inhibitor rather than a substrate of P-gp/ABCB1 thus leading uncertain about the role of this pathway [52, 54, 55]. Likewise, imatinib was reported to be either a substrate or an inhibitor of BCRP/ABCG2 [56, 57], with some reports suggesting that imatinib is only an inhibitor of BCRP/ABCG2 [58]. Ozvegy-Laczka *et al.* contributed the fact that imatinib exhibits a high-affinity interaction with BCRP/ABCG2, higher than that with P-gp/ABCB1 or MRP1/ABCC1 [57]. In accordance with this study, Hegedus *et al.* demonstrated that imatinib may interact with P-gp/ABCB1 and significantly inhibit MRP1/ABCC1-ATPase activity, but not a good substrate or inhibitor of the human MRP1/ABCC1 protein [9]. Imatinib is known to effectively stimulate the ATPase activity of BCRP/ABCG2 and P-gp/ABCB1 at low nanomolar concentrations [10, 59]. Consistent with previous reports, imatinib also showed a high affinity for BCRP/ABCG2 with low nanomolar 50% inhibitory concentration (IC_{50}) values [10, 59].

Though contradicted reports suggested that imatinib is an inhibitor rather than a substrate of ABC transporters. Dohse's study highlighted the hypothesis that both imatinib and 2 other TKIs (nilotinib and dasatinib) are substrates of P-gp/ABCB1 and BCRP/ABCG2 and at higher concentrations could also overcome transporter function. This study also suggested that therapeutic doses of imatinib may diminish the potential of both P-gp/ABCB1 and BCRP/ABCG2 to limit oral absorption or confer resistance [49]. Shukla *et al.* provided biochemical evidence that imatinib behaves as a substrate of BCRP/ABCG2 and P-gp/ABCB1 in a narrow concentration range and that at high concentrations it might act exclusively as an inhibitor due to its high affinity, a finding that is emerging as a consensus in the literature [9, 10, 56, 60, 61]. These data clearly explained why there has been significant controversy in the field regarding the potential of ABC transporters to confer drug resistance. There is clear concentration dependence determining whether imatinib assumes the phenotype of a substrate or an inhibitor.

Other than working as a substrate or an inhibitor of ABC transporters, chronic exposure of imatinib resulted significant decreases of its intracellular accumulation through up-regulated expression of P-gp/ABCB1 and BCRP/ABCG2 in Caco2 cells [62]. In another study, Nakanishi and colleagues showed that imatinib could diminish its own resistance by down-regulating BCRP/ABCG2 levels posttranscriptionally *via* the PI3K-AKT pathway [63]. And this phenomenon could only happen in BCR-ABL over-expressed cell lines such as K562/BCRP-MX10 cells; indicates that the down-regulation of BCRP/ABCG2 expression is due to the inhibitory activity of imatinib on the BCR-ABL kinase. Thereafter, Dorhse *et al.* also confirmed that imatinib could decrease BCRP/ABCG2 expression in K562-

ABCG2 cells [49]. Further studies are still required to fully elucidate the modulation effect of imatinib on the expression of ABC transporters.

Moreover, due to drug-drug interactions taking place in the MDR-ABC transporter molecular environment, imatinib is also capable of re-sensitizing resistant cells against simultaneously applied cytotoxic compounds [5]. Gao and colleagues reported that imatinib, when combined with vincristine, not only enhanced vincristine sensitivity but also significantly suppressed the tumor formation of MDR K562 cells, which overexpress P-gp/ABCB1, in a human nude mice xenograft model [64].

Oostendorp *et al.* showed that while P-gp/Abcb1 and Bcrp/Abcg2 have only modest effects on the absorption, distribution, metabolism, and excretion (ADME) of imatinib in comparison to metabolic elimination in mice. Co-administration of the P-gp/ABCB1 and/or BCRP/ABCG2 inhibitors, elacridar or pantoprazole, significantly increased the systemic exposure to imatinib in the presence or absence of P-gp/Abcb1 and/or Bcrp/Abcg2 in mice [65]. The concentrations at which imatinib inhibits the function of P-gp/ABCB1 and BCRP/ABCG2 (low micromolar concentrations) are within the known therapeutic ranges (0.1–3.4 μg/ml; 0.17–5.68 μM) of plasma levels of imatinib in patients after treatment with 25–600 mg/day [66]. Brain penetration of imatinib through the mouse BBB was demonstrated to be limited by P-gp/Abcb1 [51, 67-69] and Bcrp/Abcg2-mediated efflux [67-70]. However, P-gp/Abcb1 and Bcrp/Abcg2 function was found to only modestly affect the ADME parameters of imatinib, when administered to mice [65, 70, 71].

Some clinical studies have suggested that a threshold exists for imatinib efficacy, approximately 1000 ng/ml [72], implying that any process that reduces intracellular concentrations, particularly at the leukemic stem cell niche, could have a deleterious impact. To date, only scarce data are available regarding the involvement of MDR-ABC transporters in *in vivo* human TKI bio-distribution and toxicity, and these studies usually address the impact of the P-gp/ABCB1 or BCRP/ABCG2 polymorphic variants. Several studies reported a genotype-specific influence of P-gp/ABCB1 and BCRP/ABCG2 on the *in vivo* pharmacokinetics of imatinib [73-75]. Petain *et al.*, when investigating the effects of eight genetic polymorphisms (including those in P-gp/ABCB1, BCRP/ABCG2, CYP3A4, CYP3A5), found a prominent effect of the BCRP/ABCG2 421C>A heterozygocy on the apparent imatinib clearance [75]. Another group showed that the P-gp/ABCB1 1236C/T and 2677G/T polymorphisms were associated with altered imatinib plasma levels and, as a consequence, major differences in molecular responses to standard-dose treatment [76].

4.1.2. Nilotinib

Nilotinib (AMN107, Tasigna1) is an imatinib derivative approved by the FDA in 2007, which was developed to surmount resistance or intolerance to imatinib in patients with Philadelphia positive CML. Nilotinib is a potent, relatively selective inhibitor of the tyrosine kinase activities of BCR-ABL, PDGFR and c-KIT [77].

As the second generation of targeted BCR-ABL inhibitors entered clinical trials, continued research has produced novel data on transporter interaction patterns. Similar to imatinib, nilotinib has been shown to interact with P-gp/ABCB1 and BCRP/ABCG2. Mahon *et al.* reported that P-gp/ABCB1 was a mechanism of resistance to nilotinib and suggested that nilotinib might be a substrate of P-gp/ABCB1 [78]. Brendel *et al.* found BCRP/ABCG2-transfected K562 cells were 2- to 3-fold resistant to nilotinib and BCRP/ABCG2 could transport nilotinib at nanomolar concentrations. In addition, they also found that nilotinib was a potent inhibitor of BCRP/ABCG2 [59]. Tiwari *et al.* also reported nilotinib to be an inhibitor of both P-gp/ABCB1 and BCRP/ABCG2 by blocking the efflux function of these transporters [79]. Though Shukla *et al.* has provided evidence that nilotinib is indeed transported by P-gp/ABCB1 and BCRP/ABCG2 with *in vitro* and *ex vivo* assays [80]. However, opposing views regarding the ability of P-gp/ABCB1 or BCRP/ABCG2 to transport nilotinib have been proposed [81]. Moreover, whether nilotinib is a transported substrate for P-gp/ABCB1 is still a controversial issue [82, 83]. Nevertheless, recent reports seem to agree that at higher concentrations, nilotinib is able to inhibit the function of these transporters. They also alter the transport of simultaneously co-administrated MDR-ABC transporter substrates, most probably through drug-drug interactions [49, 59, 82].

Similar to imatinib, nilotinib could also decrease BCRP/ABCG2 expression in K562-ABCG2 cells [49]. There is no *in vivo* data available at this moment regarding the interaction of nilotinib with ABC transporter in mice or human clinical study.

4.1.3. Bosutinib

Bosutinib is a dual Src/Abl TKI, is effective and tolerable in patients with chronic phase imatinib-resistant or imatinib-intolerant CML [84, 85]. It has been granted FDA approval in 2012.

Bosutinib has been shown to inhibit P-gp/ABCB1- and BCRP/ABCG2-mediated fluorescent dye efflux. However, bosutinib was not a transported substrate for either of these transporters in the therapeutic concentration range [82]. There are no other published data indicating if bosutinib can be used to modulate and reverse BCRP/ABCG2- and P-gp/ABCB1-mediated MDR.

4.2. EGF Family TKI

4.2.1. Gefitinib

Gefitinib, approved by the FDA in 2003, was developed for treatment of the advanced or metastatic NSCLC [86, 87]. Gefitinib targets the intracellular kinase domain of the EGFR by blocking ATP binding and, as a consequence, autophosphorylation of the receptor [88].

Gefitinib was also characterized in detail with respect to its *in vitro* interaction profile with ABC transporters [89]. Amalia *et al.* suggested that the interaction of this agent with MDR proteins may be an important determinant of drug resistance [90]. Gefitinib was found to directly inhibit the transport activity of P-gp/ABCB1 and reverse P-gp/ABCB1-mediated MDR in cancer cells [91]. It has been reported that gefitinib could reduce drug resistance by acting as either an inhibitor or a substrate of BCRP/ABCG2 [92-97]. Yang *et al.* also reported that gefitinib reversed MDR mediated by both P-gp/ABCB1 and BCRP/ABCG2 [98]. However, discrepancies emerged regarding the nature of gefitinib interaction with BCRP/ABCG2. Following the initial controversies concerning whether this compound is a substrate or an inhibitor of this transporter, upcoming study confirmed that gefitinib is actively transported at lower concentrations; while at higher doses, gefitinib is not actively extruded by BCRP/ABCG2 but rather exhibited significant inhibitory activity on BCRP/ABCG2 [99]. A clinical example has been reported by Usuda et al. who presented a patient with acquired resistance to gefitinib without any mutation in the EGFR gene but a massive over-expression of the BCRP/ABCG2 protein [100].

Stewart *et al.* reported that gefitinib significantly enhanced antitumor activity and oral bioavailability of co-administrated irinotecan in mice [101]. Gefitinib also decreases the clearance and increases the oral absorption of topotecan by modulating P-gp/Abcb1 and Bcrp/Abcg2 function in mice [93]. The functional role of the mouse P-gp/Abcb1 and Bcrp/Abcg2 proteins in the brain distribution of gefitinib is also reported thereafter [102, 103]. Distribution of gefitinib to the brain is limited by P-gp/Abcb1 and Bcrp/Abcg2-mediated active efflux and the co-administration of modulators of P-gp/ABCB1 and BCRP/ABCG2 significantly increased brain uptake of gefinitib in mice [102, 103]. Gefitinib at clinically administered doses achieves plasma concentrations of 1–2 μM [104], which is in the range for inhibiting P-gp/ABCB1 and BCRP/ABCG2 functions, therefore suggesting that expression of BCRP/ABCG2 and P-gp/ABCB1 may be an important determinant for the distribution and sensitivity of gefitinib and co-administrated drugs in tumors and normal tissues.

4.2.2. Pazopanib

Pazopanib is the newest orally administered small-molecule TKI approved by FDA in 2009. As a novel and potent second generation multi-targeted TKI, pazopanib was found to target selectively VEGFR-1, -2 and -3, PDGFR-α/β and c-KIT to inhibit tumor growth and angiogenesis. Preclinical or clinical evaluation has revealed its excellent anti-angiogenic and antitumor activity in several human tumors, including renal cell carcinoma (RCC), NSCLC and gynecological tumors [105-107].

To our knowledge, there is no data available at this moment regarding the interaction of pazopanib with ABC transporters.

4.2.3. Vandetinib

Vandetanib became the first drug to be approved by FDA in 2011 for treatment of advanced medullary thyroid cancer in adult patients who are ineligible for surgery. Currently it is in phase III clinical trials for NSCLC patients. It targets VEGFR-2 (Flk-1/KDR), EGFR (ErbB1/Her-1), and rearranged during transfection (RET) tyrosine kinases. It displays antitumor activity by directly inhibiting tumor cell proliferation and survival *via* EGFR and RET inhibition, as well as tumor angiogenesis *via* VEGFR inhibition [108].

It is reported that vandetanib may act as transport substrate of BCRP/ABCG2 and as an inhibitor of P-gp/ABCB1 [90]. Another study also confirmed that vandetanib may interact with P-gp/ABCB1 and inhibit its function [109]. Zheng *et al.* showed the efficacy of

vandetanib on MRP1/ABCC1- and BCRP/ABCG2-mediated MDR *in vitro*. Vandetanib inhibited the transport function of MRP1/ABCC1 and BCRP/ABCG2 and sensitized MDR cancer cells to substrate drugs of these two transporters [110].

4.2.4. Axitinib

Axitinib is an oral, potent, small molecule ATP-competitive multi-targeted TKI approved by FDA in 2012. It inhibits cellular signaling by blocking VEGFR-1, VEGFR-2 and VEGFR-3; PDGFR; and c-KIT [111-113]. In preclinical and clinical studies, axitinib has been shown to inhibit angiogenesis, vascular permeability and blood flow. In phase II studies, axitinib showed single-agent activity in a variety of tumor types, including NSCLC [114], advanced RCC [115] and thyroid cancer [116].

Poller *et al.* studied axitinib transport using Madin-Darby canine kidney II cells over-expressing human P-gp/ABCB1 or human BCRP/ABCG2 or murine Bcrp/Abcg2 [117]. Axitinib was a good substrate of P-gp/ABCB1 and murine Bcrp/Abcg2, whereas transport activity by human BCRP/ABCG2 was moderate. These transporters may therefore contribute to axitinib resistance in tumor cells. In addition, there is another report suggested that axitinib can enhance the efficacy of conventional chemotherapeutic drugs in SP cells and BCRP/ABCG2-overexpressing MDR cells *via* directly inhibiting the drug transport function of BCRP/ABCG2 [118].

P-gp/Abcb1 strongly restricts axitinib brain accumulation and completely compensates for the loss of Bcrp/Abcg2 at the blood-brain barrier, whereas Bcrp/Abcg2 can only partially take over P-gp/Abcb1-mediated axitinib efflux. Hence, Bcrp/Abcg2 has a stronger impact on axitinib oral plasma pharmacokinetics, whereas P-gp/Abcb1 is the more important transporter at the BBB [117].

4.3. EGFR Family TKI

4.3.1. Erlotinib

Erlotinib, approved by the FDA in 2003 for the treatment of locally advanced or metastatic NSCLC, are actually under evaluation in clinical trials for other tumors [119]. Like gefitinib, erlotinib also targets the intracellular kinase domain of the EGFR by blocking ATP binding and, as a consequence, autophosphorylation of the receptor [88].

Erlotinib also interacted with some ABC transporters (e.g. P-gp/ABCB1, BCRP/ABCG2) and involved in MDR. It has been ascertained that erlotinib is substrate of these efflux pumps so that its therapeutic employment has been limited [89]. Erlotinib interacts with both P-gp/ABCB1 and BCRP/ABCG2 but not multidrug resistance protein 2 (MRP2/ABCC2), and like gefitinib, are transported only in a narrow concentration range [99, 120]. Recently, shi *et al.* reported that erlotinib could reverse P-gp/ABCB1- and BCRP/ABCG2-mediated MDR in cancer cells through direct inhibition of the drug efflux function of these two ABC transporters [121].

The systemic exposure, bioavailability and brain penetration of erlotinib has been assessed as well [120, 122]. In *in vivo* studies done in Abcb1a/b(−/−), Abcg2(−/−), Abcb1a/b(−/−)Abcg2(−/−), and Abcc4(−/−) mice, both Tellingen's and Stewart's group independently showed that both P-gp/Abcb1 and Bcrp/Abcg2 reduced the brain penetration of erlotinib and that the absence of P-gp/Abcb1 and Bcrp/Abcg2 significantly affected the oral bioavailability of this drug in mice [120, 123]. While in another human clinical study with erlotinib, there was no apparent correlation between the BCRP/ABCG2 Q141K variant and drug accumulation or TKI-induced diarrhea [124].

4.3.2. Lapatinib

Lapatinib, a reversible inhibitor of both EGFR and HER-2 tyrosine kinases, has been recently approved by the FDA in 2007 for its use in combination with Capecitabine in the treatment of advanced breast cancer over-expressing HER2 (HER2+) [125]. It has also been reported that lapatinib was effective as a single agent or in combination with other chemotherapeutic drugs in HER2-overexpressing and/or possibly EGFR-expressing endometrial cancer [126].

It was reported that lapatinib was a substrate for P-gp/ABCB1 and BCRP/ABCG2, as well as an inhibitor of P-gp/ABCB1 and BCRP/ABCG2 with IC_{50} values of 3.9 μM and 0.025 μM, respectively [127]. Perry *et al.* showed that lapatinib has a direct inhibitory effect on BCRP/ABCG2 accounting for the synergistic findings. The synergy is cell line dependent and related to the activity of specific efflux pumps [128]. Dai *et al*. also confirmed that lapatinib could reverse P-gp/ABCB1- and BCRP/ABCG2-mediated MDR by directly inhibiting their transport function, but it did not affect the expression of mRNA and protein levels of both transporters [129]. Molina *et al.* found that lapatinib increased the accumulation and cytotoxicity of topotecan in cells that overexpressed P-gp/ABCB1 or

BCRP/ABCG2 [130]. The highest peak plasma level of lapatinib was reported to be ~3 μM in human pharmacokinetic studies, which is in the range for inhibiting P-gp/ABCB1 and BCRP/ABCG2 functions [131].

In two *in vivo* studies, Polli *et al.* showed that lapatinib is a substrate of both P-gp/Abcb1 and Bcrp/Abcg2, and these two transporters work in combination to modulate the CNS penetration of lapatinib in mice, resulting in a 40-fold increase in brain-to-plasma ratio in Abcb1a/b(−/−), Abcg2(−/−) mice compared with wild-type mice [127, 132]. Lapatinib also strongly enhanced the inhibitory effect of paclitaxel on the growth of a cancer xenograft in nude mice that overexpressed P-gp/Abcb1 [129]. These *in vivo* studies further confirmed that lapatinib could either be a substrate or an inhibitor of P-gp/ABCB1 or BCRP/ABCG2.

4.4. Multi-Targets TKI

4.4.1. Sorafenib

Sorafenib is a multi-kinase inhibitor with a similar target kinase spectrum approved by FDA in 2005 for the treatment of patients with advanced RCC and hepatocellular carcinoma [133].

Results from studies investigating the interaction of sorafenib with efflux transporters have suggested that sorafenib is minimally transported by P-gp/ABCB1 or BCRP/ABCG2 [134]. Lagas *et al.* also reported that sorafenib is a moderate P-gp/ABCB1 substrate, whereas sorafenib is more efficiently transported by BCRP/ABCG2 and murine Bcrp/Abcg2 [135]. Another *in vitro* study also showed that BCRP/ABCG2 has a high affinity for sorafenib. But for P-gp/ABCB1, sorafenib did show inhibition on its transport activity, but did not seem to be a substrate of it [136]. The *in vivo* pharmacokinetic studies performed in KO mice showed similar results. The function of mouse P-gp/Abcb1 and Bcrp/Abcg2 significantly influenced the brain accumulation of sorafenib [134, 135, 137], with Bcrp/Abcg2 being the dominant chemo-protective transporter at the BBB [135]. Furthermore, in P-gp/Abcb1 KO mice, transporter-related interaction did not alter the plasma systemic pharmacokinetics of sorafenib [134, 137].

4.4.2. Sunitinib

Sunitinib is an orally administered small-molecule multi-target kinase inhibitor. It potently inhibits the VEGFR, PDGFR, c-KIT and other receptors such as FLT3, and colony stimulating factor-1 receptor (CSF-1R) [138, 139]. Sunitinib is approved in 2012 for the treatment of advanced RCC and imatinib-resistant gastrointestinal stromal tumors [140].

Sunitinib was reported to induce conformational changes or interact at the substrate-binding pocket of P-gp/ABCB1 and BCRP/ABCG2, thereby partially and completely reversing P-gp/ABCB1- and BCRP/ABCG2-mediated MDR, respectively, at a nontoxic concentration of 2 μM [141]. While recent reports have also established that sunitinib is recognized, bound and in a specific concentration window can also be effluxed by both P-gp/ABCB1 and BCRP/ABCG2 [141, 142]. In a recent multi-center pharmacogenetic association study involving 219 patients treated with sunitinib as a single agent, polymorphisms of P-gp/ABCB1 and BCRP/ABCG2 have been shown to be associated with sunitinib-induced toxicity [143]. However, Hu *et al.* suggest that sunitinib does not appear to be a high-affinity substrate for P-gp/ABCB1 or BCRP/ABCG2. Furthermore, the absence of P-gp/Abcb1 in mice had no effect on the plasma pharmacokinetics of sunitinib but significantly influenced its brain accumulation [134]. Therefore, further experiments are still needed to determine whether P-gp/ABCB1 and/or BCRP/ABCG2 contribute to the clinical MDR to sunitinib.

4.4.3. Dasatinib

Dasatinib is a dual-function Src/ABL tyrosine kinase inhibitor approved by the FDA in 2006. It has shown clinical benefit and tolerability in patients in all phases of CML, as well as in those with Philadelphia chromosome-positive ALL [144]. It also inhibits the ephrin family of kinases, including PDGFR and c-KIT [145].

Dasatinib has been described as a substrate of P-gp/ABCB1 and BCRP/ABCG2 but only as a weak modulator of P-gp/ABCB1 [146-148]; while no data regarding modulation of BCRP/ABCG2 or MRP1/ABCC1 are available. Dohse's study further confirmed that dasatinib is substrates of P-gp/ABCB1 and BCRP/ABCG2 [49]. In addition to P-gp/ABCB1, dasatinib could also overcome transport function of BCRP/ABCG2 at higher concentrations [49]. All these evident showed that dasatinib is substrate of P-gp/ABCB1 and BCRP/ABCG2. When dasatinib is applied at higher concentration, it is able to inhibit function of these two transporters and alters the transport of simultaneously applied ABC transporters' substrates [49, 82]. Dasatinib could also decrease ABCG2 surface expression in K562-ABCG2 cells. In

comparison to imatinib and nilotinib, dasatinib showed more potent down-regulation activity in reducing BCRP/ABCG2 expression [49].

In vivo brain distribution studies showed that the brain distribution of dasatinib significantly increased in Mdr1a/b(-/-) and Mdr1a/b(-/-) Bcrp1(-/-) mice [11]. In another study, oral uptake of dasatinib was shown to be significantly limited by murine P-gp/Abcb1 and the function of this transporter was shown to be the primary determinant of the restricted brain accumulation of dasatinib. While Bcrp/Abcg2 could only partly restrict brain accumulation of dasatinib at the BBB [148]. Furthermore, the penetration of dasatinib across the BBB is influenced by the presence of the inhibitors of P-gp/Abcb1 and Bcrp/Abcg2 [11, 148].

4.5. Other New PKI

4.5.1. Crizotinib

Crizotinib is an oral small-molecule receptor tyrosine kinases (RTK) inhibitor that targets anaplastic lymphoma kinase (ALK) and hepatocyte growth factor receptor (HGFR; MET), and potentially other RTKs. It was approved by the FDA in 2011 for the treatment of ALK-rearranged NSCLC [149].

The Studies concerning the interaction of crizotinib with ABC transporter is limited. Crizotinib significantly enhanced the cytotoxicity of chemotherapeutic agents that are substrates of P-gp/ABCB1. Additionally, it reversed P-gp/ABCB1 mediated MDR by inhibiting P-gp/ABCB1 transport function without affecting P-gp/ABCB1 expression or blocking the Akt or ERK1/2 pathways [150].

4.5.2. Vemurafenib

Vemurafenib received FDA approval in 2011 for the treatment of $BRAF^{V600E}$-positive malignant melanoma. Vemurafenib is a small-molecule serine threonine kinase inhibitor of BRAF and its action blocks the mutated $BRAF^{V600E}$ and its abnormal activation of the MAP kinase pathway [151, 152]. In the initial Phase I testing of the drug, the overall response rate was 76% (37 out of 49 patients with mutated BRAFV600E responded) and 34 (69%) had a partial response while three (6%) had a complete response [153]. This impressive result led to a pivotal Phase III trial comparing vemurafenib plus dacarbazine versus dacarbazine alone showing that overall survival at 6 months was 84 versus 64%, and the median progression-free survival was 5.3 versus 1.6 months, respectively [154]. The clinical data indicate that vemurafenib is efficacious against malignant melanoma.

The study regarding the interaction of vemurafenib with ABC transporter is also limited. Study performed *in vitro* with MDCKII cells that over-express human P-gp/ABCB1 or murine Bcrp/Abcg2 revealed that vemurafenib is a substrate for the two efflux transporters [155]. *In vivo* study has also shown that the brain distribution of vemurafenib is severely restricted at the BBB because of active efflux by both P-gp/Abcb1 and Bcrp/Abcg2 in mice [155].

4.5.3. Ruxolitinib

Ruxolitinib, a potent dual inhibitor of the JAK1 and JAK2 from Incyte Corporation was initially tested in patients with either JAK2-V617F negative or JAK2-V617F positive myeloproliferative disorder (MPD). It was approved as the first JAK inhibitor by FDA in 2011 for the treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, postpolycythemia vera myelofibrosis, and postessential thrombocythemia myelofibrosis [156-158]. Interestingly, ruxolitinib is efficacious even in myelofibrosis patients with no JAK2 mutations, presumably indicating that these inhibitors act on kinases besides JAK2, re-emphasizing the potential of multi-kinase inhibitors [159].

To our knowledge, there is no data available at this moment regarding the interaction of ruxolitinib with ABC transporter.

5. CONCLUSION

The emergence of drug resistance to targeted cancer therapies is an ongoing clinical problem. While resistance or altered pharmacokinetics to small-molecule PKIs can be caused by their interactions with drug efflux ABC transporters and uptake transporters at the physiological barriers in the body, it present further challenges concerning potency and selectivity. In this review, we summarized the detailed information on the interaction of each FDA-approved small molecular PKI with ABC transporter (Table **2**). MDR-ABC transporters actively extrude and consequently reduce the targeted anticancer effects of several transporter substrate PKIs at the cellular and tissue barriers. Each of these transporter substrate PKIs is an interacting partner of at least one of the major MDR-ABC transporters. Several PKIs, especially at higher concentrations, directly inhibit MDR-ABC transporters, while they function as substrates of the major MDR-ABC transporters at lower

Table 2: Summary of Interaction of 15 FDA Approved PKIs with ABC Transporters

No	Name	Major Targets	P-gp/ ABCB1	BCRP/ ABCG2	MRP1/ ABCC1	Verification in *in vivo* study		References
						Animal study	Human clinical study	
1	Imatinib	BCR-ABL	S, I	S, I	I (W)	YES	YES	[9, 10, 49, 51-71]
2	Nilotinib	BCR-ABL	S, I	S, I	N/A	N/A	N/A	[49, 59, 78-83]
3	Bosutinib	BCR-ABL/SRC	I (W)	I (W)	N/A	N/A	N/A	[82]
4	Gefitinib	EGFR	I	S, I	N/A	YES	YES	[89-99, 101-104]
5	Pazopanib	VEGFR2/PDGFR/c-KIT	N/A	N/A	N/A	N/A	N/A	N/A
6	Vandetanib	EGFR/VEGFR/RET	I	S, I	I	N/A	N/A	[90, 109, 110]
7	Axitinib	VEGFR1,2,3/PDGFRB/c-KIT	S	S, I	N/A	YES	N/A	[117, 118]
8	Erlotinib	ErbB1	S, I	S, I	N/A	YES	NO	[89, 99, 120-123]
9	Lapatinib	ErbB1/ErbB2	S, I	S, I	N/A	YES	NO	[89, 127-132]
10	Sorafenib	Multiple Targets	S (L), I	S, I	N/A	YES	NO	[134-137]
11	Sunitinib	Multiple Targets	S, I	S, I	N/A	YES	YES	[134, 141, 142]
12	Dasatinib	Multiple Targets	S, I (W)	S, I (W)	N/A	YES	NO	[11, 49, 82, 146-[148]
13	Crizotinib	ALK/MET	I	N/A	N/A	N/A	N/A	[150]
14	Vemurafenib	BRAF	S	S	N/A	YES	N/A	[155]
15	Ruxolitinib	JAK	N/A	N/A	N/A	N/A	N/A	N/A

S-substrate; I-inhibitor; S (L)-substrate (low affinity); I (W)-inhibitor (weak inhibition); N/A-no data available.

concentrations. *In vivo* animal studies are based on the human and the rodent orthologs of the given transporters that have conserved function and identical substrate and inhibitor recognition spectra. However, species differences might affect the expression, tissue distribution and drug interaction patterns of the drug transporters. While for clinical cancer patients, we still need a detailed database providing accessible data for the kinetic parameters of the PKIs-transporter interactions, the basic level of transporter expression in the relevant cell types and tissue barriers, as well as information for the effects of major ABC transporter.

Similar to the conventional anti-cancer chemotherapeutics, the recognition of PKIs by ABC transporters as specific substrate will also be an obstacle to the targeted anti-cancer therapy. Though the mechanism is still unclear, some PKIs demonstrated to be good MDR modulators and reversed MDR in cancer cells. PKIs including gefitinib, lapatinib, erlotinib and vandetanib shared the base structure with derivatives of quinazolines, which are the most promising ATP competitive protein tyrosine kinase inhibitors (Figure **1**). All these 4 PKIs demonstrated potent inhibitory effects on the function of ABC transporters and reversed MDR in cancer cells. Some critical structures other than quinozaline might also play important role in the ATP competitive mechanism. Given that most of PKIs are type I inhibitors and competitively inhibit the access of ATP to the binding pocket on protein kinases, the competitive binding of these PKIs to the ATP-binding sites of ABC transporters could be one possible MDR modulation mechanism of PKIs. Furthermore, the direct inhibitory effects of PKIs on the ATP hydrolysis or the specific recognition of the substrate of ABC transporters could be other possible mechanism as well. But, it is still need more studies to clarify the detailed mechanism regarding some specific PKI could only inhibit the function of one ABC transporter but other PKI could inhibit the function of two or more different ABC transporters.

The reciprocal interactions of PKIs and ABC transporters (such as ABCB1/P-gp and ABCG2/BCRP) might work in three different modes as shown in Figure **2**. (a) PKIs can be substrates of ABC transporters and can be actively efflux from cells. (b) PKIs can be inhibitors of ABC transporters and actively inhibit efflux activity of ABC transporters. (c) PKIs can regulate the expression level of ABC transporters, either directly increase the expression level of ABC transporters or

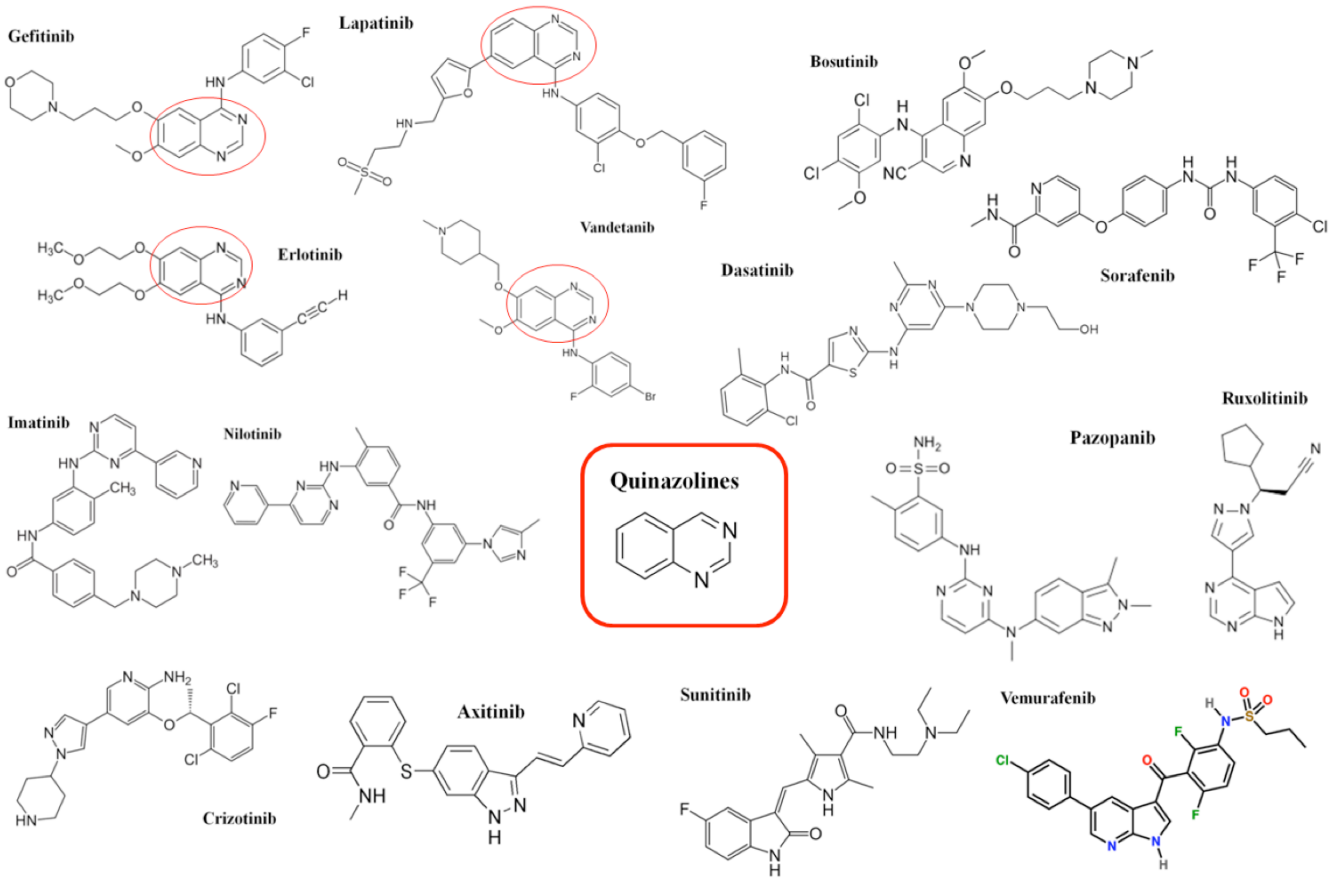

Figure 1: Chemical structures of 15 FDA approved PKIs and the base structure of quinazolines. Four PKIs including gefitinib, lapatinib, erlotinib and vandetanib shared the base structure with derivatives of quinazolines, which are the most promising ATP competitive protein tyrosine kinase EGFR inhibitors.

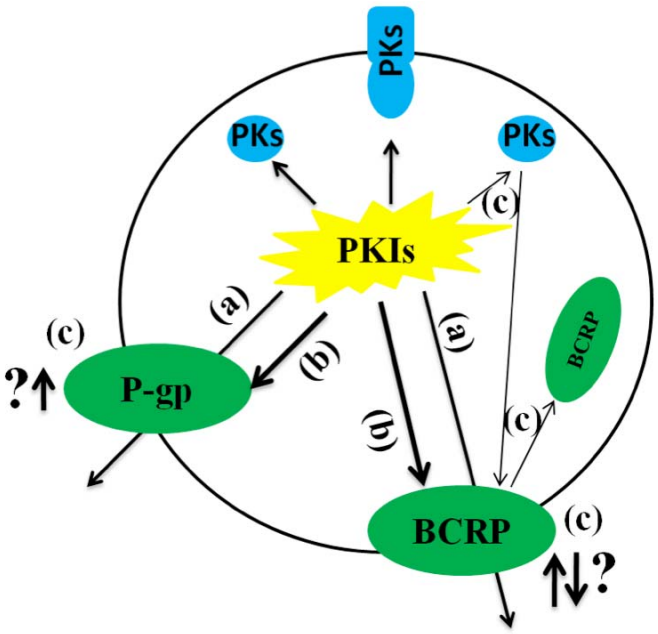

Figure 2: Schematic Representation of reciprocal interactions of PKIs with ABC Transporters (ABCB1/P-gp and ABCG2/BCRP). (a) PKIs can be substrates of ABC transporters and can be actively efflux from cells. (b) PKIs can be inhibitors of ABC transporters and actively inhibit efflux activity of ABC transporters. (c) PKIs can regulate the expression level of ABC transporters, either directly increase the expression level of ABC transporters or indirectly stimulate relocalisation and decrease expression level of ABC transporters (such as ABCG2/BCRP) through their regulatory activity on PKs.

indirectly stimulate relocalisation and decrease expression level of ABC transporters (such as ABCG2/BCRP) through their regulatory activity on protein kinase.

Several PKIs could be actively transported by ABC transporters, thus it is possible to increase their bioavailability and efficacy by co-administering a non-toxic modulator of these transporters. In the future, further studies using more advanced technologies are still needed to elucidate how PKIs interact with the major ABC transporters in cancer cell lines, animals as well as cancer patients. These studies will provide more and more detailed information on PKI-ABC transporter interaction and help in the developing better clinical application of PKIs in various cancer patients. It will also help in the developing of new generation of PKI-based therapy that could more effectively and selectively treat various ABC transporter over-expressing cancers.

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