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Invited review

The importance of breast cancer resistance protein to the kidneys excretory function and chemotherapeutic resistance

Pedro Caetano-Pinto[a], Jitske Jansen[a], Yehuda G. Assaraf[b], Rosalinde Masereeuw[a,*]

[a] Division of Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Universiteitsweg 99, Utrecht 3584 CG, The Netherlands
[b] The Fred Wyszkowski Cancer Research Laboratory, Department of Biology, Technion-Israel Institute of Technology, Haifa, Israel

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ABSTRACT

The relevance of membrane transporters gained momentum in recent years and it is now widely recognized that transporters are key players in drug disposition and chemoresistance. As such, the kidneys harbor a variety of drug transporters and are one of the main routes for xenobiotic excretion. The breast cancer resistance protein (BCRP/*ABCG2*) is widely accepted as a key mediator of anticancer drug resistance and is a prominent renal drug transporter. Here, we review the role of BCRP in both processes and present a multitude of variables that can influence its activity. An increasing number of renally cleared chemotherapeutics, including tyrosine kinase inhibitors, described as BCRP substrates can modulate its activity via transcription factors and cellular signaling pathways, such as the phosphoinositide 3-kinase (PI3K) pathway. In addition to pharmacological actions, genetic variations, as well as differences between species and gender can affect BCRP function, which are also discussed. Furthermore, the role of BCRP in light of cancer treatments and the implications for novel therapeutic interventions that take into account renal function are discussed.

Contents

1. Introduction

Transporters are key players in drug disposition, with active roles in excretion, drug-drug interactions and other pharmacologically relevant interactions, such as drug-nutrient or drug-toxicant interactions, thereby influencing the concentration of the drug at the target site (Konig et al., 2013). Our understanding of the role played by transporters and their contribution to physiological processes has gone beyond the classical view where these mechanisms were merely responsible for translocating substrates from the cytoplasm to extracellular compartments and *vice versa* (International Transporter et al., 2010). Xenobiotic transporters are implicated in many processes, including intestinal absorption, maintenance of blood-organ barriers – including the brain, testis and placenta, – bile secretion in the liver, as well as in renal function, where the overwhelming majority of xenobiotics and metabolic bi-products are excreted via active membrane transport (Konig, et al., 2013; Nigam, 2015).

* Corresponding author.
E-mail address: r.masereeuw@uu.nl (R. Masereeuw).

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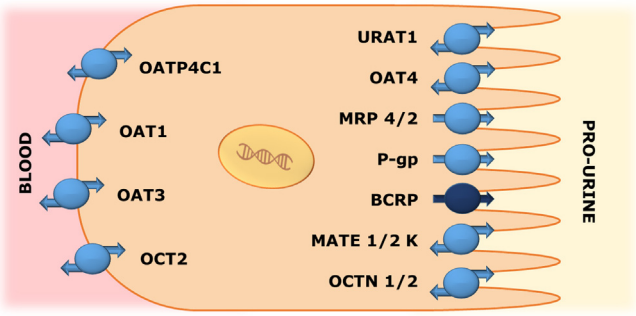

Fig. 1. Drug transporters in the proximal tubule. Influx transporters facing the blood side: organic anion transporter protein 4C1 (OATP4C1), organic anion transporter 1 and 3 (OAT1 and −3) and organic cation transporter 2 (OCT2). Efflux Transporters expressed at the apical membrane – urate anion exchanger 1 (URAT1), OAT4, multidrug resistance protein 2 and 4 (MRP2 and −4), and P-glycoprotein (P-gp). Breast cancer resistance protein (BCRP), multidrug and toxin extrusion protein 1 and 2K (MATE1 and −2K) and the organic carnitine transporter 1 and 2 (OCTN1 and −2). Solute carrier transporters (SLCs) are depicted as ⇐⇒, and ATP binding cassette (ABC) transporters as ⊂⇒.

The kidneys are responsible for a variety of key regulatory functions that are tightly associated with other physiological processes. These include regulation of physiological pH by maintaining appropriate acid-base homeostasis, generation of hormones responsible for stimulating the production of red blood cells and regulation of blood pressure by controlling the volume of body fluids. The kidneys are also responsible for nutrient reabsorption and the hallmark of renal function is their excretory role of endo- and xenobiotics from the peritubular capillaries into the pro-urine. (Masereeuw et al., 2014). The properties that enable renal transporters to mediate drug excretion are also of paramount importance in chemotherapeutic drug resistance. Although physiologically distinct, cancer drug resistance and renal excretion both rely on active (i.e. ATP-driven) membrane transport, via multidrug resistance efflux transporters of the ABC superfamily.

A myriad of factors contribute to chemoresistance, as cancers are inherently heterogeneous, and their genetic instability can facilitate the acquisition of drug resistance either to cope directly with cytotoxic drugs or to recover from their effects (Ifergan et al., 2005; Gonen and Assaraf, 2012; Ferreira et al., 2016; Li et al., 2016; Wijdeven et al., 2016; Zhitomirsky and Assaraf, 2016). Cell survival mechanisms can be hijacked, growth pathways permanently activated, or the DNA repair machinery enhanced, thereby reducing cellular sensitivity to DNA damage (Jeggo et al., 2016). Programmed cell death cascades can become altered or silenced, rendering cancer cells resistant to toxic stress. Further, metabolic processes and enzymatic activities are upregulated and adapted in order to cope with high bioenergetics demands stemming from accelerated growth (Li et al., 2016; Wijdeven et al., 2016). Chemotherapy by itself can promote or enhance drug resistance phenotypes. This phenomenon arises when cancer cells alter their homeostasis by modifying gene expression or re-routing signaling pathways as a response to drugs targeting particular cellular processes. Drugs can also exert selective pressure in the cancer microenvironment, favoring the growth of subpopulations with constitutive resistance genes or that adapt to harness such mutations (Holohan et al., 2013). This plasticity, derived from their genomic instability, is a major enabler of cancer chemoresistance.

On top of these effects, multidrug efflux pumps expel a wide spectrum of structurally and mechanistically distinct chemotherapeutic agents from tumors, hence limiting their cytotoxic potential. Given the plethora of factors contributing to cancer chemoresistance (Gonen and Assaraf, 2012; Ferreira et al., 2016; Li et al., 2016; Raz et al., 2016; Wijdeven et al., 2016; Zhitomirsky and Assaraf, 2016), multidrug efflux transporters are just a component of a fairly large array of mechanisms of chemoresistance. Nonetheless, since the original description of a multidrug resistance (MDR) protein, *P*-glycoprotein (P-gp, *ABCB1*), the body of evidence validating the role of membrane transporters in poor cancer drug response has markedly expanded (Fletcher et al., 2016). The additional depiction of P-gp in adult organs, including the kidneys, and the discovery of a myriad of other drug transporters, cemented the role of these transporter proteins in drug resistance and excretion. The breast cancer resistance protein (BCRP/ABCG2), has been increasingly implicated in the handling of renal clearance of metabolites and relevant therapeutic drugs, including many chemotherapeutic agents. In the kidneys BCRP expressed at the apical membrane along with other MDR efflux transporters, including P-gp, with great substrate promiscuity between them and consequent functional redundancy in urinary excretion. In the current review, we present the role of BCRP regarding both kidney function and cancer MDR.

2. Renal transporters and drug excretion

In the process of removing solutes from the systemic circulation, following glomerular filtration, water, nutrients and salts are reabsorbed to prevent losses, whereas xenobiotics such as drugs and environmental toxicants, as well as metabolic bi-products, endogenous wastes, must be removed from the bloodstream and concentrated in the urine. This latter process takes predominantly place at the proximal tubule epithelium (PTE), which expresses multiple membrane transporters, as well as an array of phase I and phase II metabolism enzymes. Together, these elements render PTE cells (PTEC) crucial for disposition of xenobiotics. PTEC are highly polarized and specialized cells that consist of two surfaces, one exposed to the interstitium, thus surrounded by a network of capillaries, and another exposed to the tubular lumen and covered with microvilli, forming a brush-border membrane with a large surface area (Fig. 1). This polarization of cells enables them to act as a selective barrier, where solutes, ions, drugs, metabolites and other compounds can be shuttled unidirectionally either back to the circulation or into the pre-urine. Membrane-bound carrier proteins are responsible for the selective nature of transport in PTE, by binding substrates in order to relocate them. These proteins can be divided into ion channels, solute carriers, aquaporins or efflux pumps. With regard to drug excretion, efflux pumps belonging to two families are pivotal to the process.

The Human genome organization (HUGO; http://www.genenames.org) reports a highly diverse group of membrane transport proteins that includes over 300 entries, *viz.* the solute carrier (SLC) family. A number of these carriers are expressed in the PTE, providing specificity for different classes of drugs, as well as metabolites and nutrients; these transporters are involved in both excretion and reabsorption of solutes. SLC transporters facilitate the uptake of xenobiotics from the interstitium and a range of substrates including negatively charged solutes handled by organic anion transporters 1 and 3 (OAT1, *SLC22A6* and OAT3, *SLC22A8*, respectively), as well as the organic anion transporter polypeptide 4C1 (solute carrier organic anion transporter family member 4A1; *SLCO4C1*) (Nigam et al., 2015). Alongside, the organic cation transporter 2 (OCT2; *SLC22A1*) handles positively charged solutes. The apical side of PTEC faces the lumen of the nephron and a set of transporters present at this side extrude solutes, drugs, metabolic bi-products and other compounds into the ultra-filtrate, a process which concentrates xenobiotics and metabolic waste compounds in the urine. Present at this side are the multidrug and toxin extrusion protein 1 and 2 (MATE1 (*SLC47A1*) and MATE2K

Table 1
List of FDA approved drugs that are eliminated via the renal route and have been described as substrates for BCRP. Most of these 49 compounds are also substrates for other transporters expressed in the kidney, being P-gp the most common and chemotherapeutical agents are the majority, with 25 substrates. Any known pharmacological interactions between these substrates and BCRP are also listed in the table (known interactions). The majority of the described interactions involve changes in the of plasma levels of a given substrate when co-administrated, the compounds marked with * increase in plasma levels, while compounds marked with ** decrease in plasma levels. Unknown parameters are designated not defined (n/d). Data retrieved from drugbank.ca.

			Substrate for		
Drug	Class	Renal clearance	basolateral	apical	Known interactions
Apixaban	Anticoagulant	27%	n/d	P-gp	Imatinib*, Idelalisib*, Dabrafenib**
Buprenorphine	Analgesic	10–30%	n/d	P-gp	Dabrafenib**, Idelalisib*
Carboplatin	Chemotherapeutical agent	100%	n/d	MRP2	Topotecan, Paclitaxel
Cisplatin	Chemotherapeutical agent	100%	OCT2	hMATE I, hMATE II	Docetaxel, Paclitaxel, Topotecan
Clofarabine	Chemotherapeutical agent	49–60%	n/d	n/d	n/d
Cyclosporine	Immunosuppressant	6%	OAT1	P-gp, MRP2	Dabrafenib**, Doxorubicin, Etoposide, Glyburide, Imatinib*, Idelalisib*, Ezetimibe*, Methotrexate*, Mycophenolate mofetil, Rosuvastatin, Pravastatin, Pitavastatin, Topotecan, Testosterone,
Daclatasvir	Antiviral	6.6%	n/d	P-gp	Dabrafenib*, Doxorubicin, Pitavastatin, Pravastatin, Topotecan, Verapamil
Dabrafenib	Chemotherapeutical agent	23%	OAT1	P-gp	Vandetanib, Teniposide, Apixaban, Buprenorphine, Cyclosporine, Doxorubicin, Estradiol, Etoposide, Imatinib, Idelalisib*, Topotecan, Sunitinib, Teniposide,
Daunorubicin	Chemotherapeutical agent	25%	OCT2	P-gp, MRP2	Verapamil*, Paclitaxel,
Docetaxel	Chemotherapeutical agent	6%	n/d	P-gp, MRP2	Cisplatin, Dabrafenib*, Sorafenib*, Verapamil*
Doxorubicin	Chemotherapeutical agent	5–12%	n/d	P-gp, MRP2	Cyclosporine*, Daclatasvir*, Idelalisib*, Paclitaxel, Zidovudine, Sofosbuvir*, Sorafenib*, Sunitinib, Vandetanib*
Dronabinol	Psychoactive drug	n/d	n/d	P-gp	Fluorouracil*, Imatinib*
Erlotinib	Chemotherapeutical agent	8%	n/d	P-gp	Dabrafenib*, Idelalisib*, Omeprazole*, Rabeprazole*
Estradiol	Steroid hormone	n/d	OCT2, OAT3	P-gp	Dabrafenib**, Glyburide, Teriflunomide**, Verapamil*
Etoposide	Chemotherapeutical agent	56%	n/d	P-gp, MRP2	Cyclosporine, Idelalisib*, Dabrafenib**, Verapamil*
Ezetimibe	Statin (anti-cholesterol)	11%	n/d	P-gp, MRP2	Cyclosporine
Fluorouracil	Chemotherapeutical agent	20–90%	n/d	MRP4	Dronabinol
Glyburide	Anti-hyperglycemic agent	n/d	OAT1	P-gp, MRP2	Cyclosporine, Dabrafenib, Estradiol, Hydrocortisone, Sunitinib, Testosterone
Hydrocortisone	Anti-inflammatory agent	n/d	n/d	P-gp	Glyburide, Testosterone, Verapamil*
Idelalisib	Chemotherapeutical agent	14%	n/d	P-gp	Apixaban, Buprenorphine, Cyclosporine, Dabrafenib, Doxorubicin, Docetaxel, Etoposide, Erlotinib, Imatinib, Irinotecan, Sunitinib, Vincristine, Verapamil, Teniposide, Sorafenib
Imatinib	Chemotherapeutical agent	5–13%	OCT2		Cyclosporine, Dronabinol, Idelalisib*, Apixaban, Dabrafenib*, Doxorubicin, Topotecan
Irinotecan	Chemotherapeutical agent	25–50%	n/d	P-gp, MRP4	Dabrafenib* , Erlotinib*, Idelalisib*, Lenvatinib*, Regorafenib*, Verapamil*
Lamivudine	Anti-viral	5%	OCT2, OAT1	P-gp	n/d

Table 1 (*Continued*)

Drug	Class	Renal clearance	Substrate for		Known interactions
			basolateral	apical	
Lansoprazole	Proton pump inhibitor	33%	n/d	P-gp	Dabrafenib**, Imatinib, Methotrexate, Mycophenolate mofetil,
Lenvatinib	Chemotherapeutical agent	25%	n/d	P-gp	Irinotecan
Methotrexate	Chemotherapeutical agent	80–90%	OAT1, OAT3	MRP2, MRP4	Cyclosporine*, Lansoprazole*, Pantaprazol*, Teriflunomide*, Verapamil*
Mycophenolate mofetil	immunosuppressive agent	93%	n/d	P-gp, MRP2	Cyclosporine**, Lansoprazole*, Pantaprazol*, Omeprazole*, Teriflunomide*
Omeprazole	Proton pump inhibitor	77%	n/d	P-gp	Cyclosporine, Erlotinib, Dabrafenib**, Mycophenolate mofetil,
Oxaliplatin	Chemotherapeutical agent	54%	OCT2	MRP2	Paclitaxel, Topotecan
Paclitaxel	Chemotherapeutical agent	14%	n/d	P-gp, MRP2	Cisplatin, Carboplatin, Oxaliplatin, Daunorubicin, Dabrafenib**, Doxorubicin, Verapamil*
Pantaprazol	Proton pump inhibitor	71%	n/d	P-gp	Erlotinib, Methotrexate, Mycophenolate mofetil, Topotecan
Pitavastatin	Statin (anti-cholesterol)	15%	n/d	P-gp, MRP2	Cyclosporine*, Daclatasvir*, Teriflunomide*
Pravastatin	Statin (anti-cholesterol)	47%	OAT1, OAT3	P-gp, MRP2	Cyclosporine*, Daclatasvir*, Teriflunomide*
Rabeprazole	Proton pump inhibitor	90%	n/d	n/d	Dabrafenib**, Erlotinib
Regorafenib	Chemotherapeutical agent	19%	n/d	P-gp	Dabrafenib**, Irinotecan, Verapamil
Rosuvastatin	Statin (anti-cholesterol)	28%	n/d	MRP4	Cyclosporine*
Sofosbuvir	Antiviral	80%	n/d	P-gp	Doxorubicin, Vincristine**, Verapamil*
Sorafenib	Chemotherapeutical agent	19%	n/d	P-gp, MRP2, MRP4	Carboplatin, Docetaxel, Doxorubicin, Idelalisib*, Paclitaxel
Sunitinib	Chemotherapeutical agent	16%	n/d	MRP4	Testosterone, Topotecan, Idelalisib*, Doxorubicin, Verapamil,
Teniposide	Chemotherapeutical agent	4–12%	n/d	n/d	Idelalisib*, Verapamil*
Teriflunomide	Immunomodulatory agent	23%	n/d	n/d	Zidovudine, Topotecan, Pravastatin, Pitavastatin, Mycophenolate mofetil, Methotrexate, Estradiol
Testosterone	Steroid hormone	90%	OAT3	P-gp	Cyclosporine, Glyburide, Hydrocortisone, Sunitinib
Topotecan	Chemotherapeutical agent	73%	n/d	P-gp	Cisplatin, Carboplatin, Cyclosporine*, Daclatasvir*, Imatinib*, Pantaprazol*, Oxaliplatin, Teriflunomide*, Vandetanib*
Vandetanib	Chemotherapeutical agent	25%	n/d	n/d	Doxorubicin, Topotecan, Verapamil
Verapamil	Anti-arrhythmia agent	70%	OCTN2	P-gp, MRP4	Apixaban, Cyclosporine, Idelalisib*, Daclatasvir*, Doxorubicin, Etoposide, Estradiol, Imatinib, Irinotecan, Methotrexate, Vincristine, Vandetanib*, Sunitinib*
Vincristine	Chemotherapeutical agent	10–20%	OCT3	MRP2	Cyclosporine*, Idelalisib*, Dabrafenib*, Sunitinib*, Verapamil*
Vismodegib	Chemotherapeutical agent	4%	n/d	P-gp	n/d
Zidovudine	Antiviral	29%	OCT2, OAT1, OAT3	P-gp, MRP4	Doxorubicin, Teriflunomide*

[1] Substrates for this transporters in addition to BCRP.

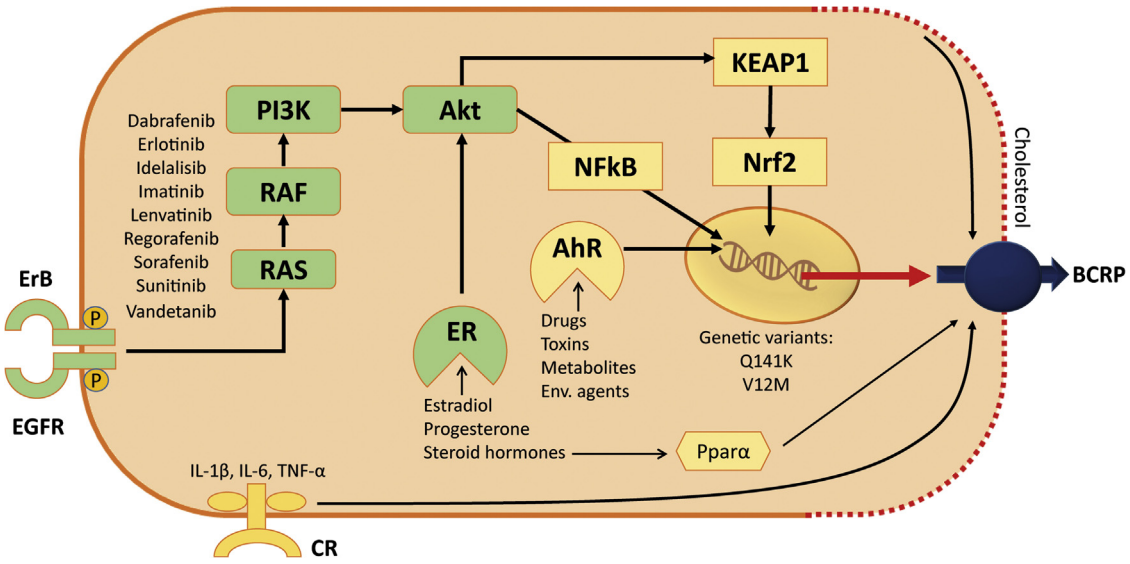

Fig. 2. Proposed BCRP regulatory mechanisms. The estrogen (ER) and aryl hydrocarbon (Ahr) are intracellular receptors that sense exogenous hormones and stimuli that can trigger a transcriptional response, via the serine-threonine protein kinase (Akt) and further the Kelch-like ECH-associated protein 1 (KEAP1) and nuclear factor erythroid-derived 2 (Nrf2), which is known to upregulate BCRP expression. Epidermal growth factor receptor (EGFR/HERB)-dependent signaling can be inhibited, upstream or downstream of the receptor, modulating the Akt cascade and resulting in BCRP suppression or activation. Gaps persist in the understanding of the full mechanism/path involved in lipid-dependent regulation, where the peroxisome proliferator-activated receptor (PPARα) receptor is involved, as well as how cytokines influence activity, acting via chemokine receptors (CR).

(*SLC47A2*), respectively), both of which share cationic substrates. Bi-directional SLC transporters are also present at the apical side, like the urate transporter (URAT1, *SLC22A12*) that exchanges anions by urate, regulating its plasma levels. The organic anion transporter 4 (OAT4, *SLC22A11*) is responsible for the reabsorption of anionic solutes and the carnitine transporters 1 and 2 (OCTN1, *SLC22A4* and OCTN2, *SLC22A5*; respectively) reabsorb this essential amino acid.

The most prominent apical efflux transporters in the PT belong to the ABC superfamily and handle the bulk of renally excreted compounds. This transporter family is highly conserved with diverse classes of trans-membrane transporter proteins, sometimes translocating substrates against steep concentration gradients, harnessing energy from ATP hydrolysis (Vasiliou et al., 2009). The HUGO lists 51 human genes encoding for ABC transporters that have been identified and classified into 7 families (ABC – A through G), according to their divergent evolution (http://www.genenames.org). Members of the ABC superfamily display broad substrate specificities and are involved in the transport of endogenous compounds like inorganic anions, metal ions, amino acids, hormones, fatty-acids, peptides, sugars and metabolic bi-products, as well as exogenous substrates such as drugs and environmental toxicants. The signature feature of this transporter superfamily is a nucleotide-binding domain (NBD), shared by all superfamily members. Traditionally, ABC transporters have been tightly associated with cancer MDR, one of the most widely studied membrane transport-related mechanisms, from which several transporters derive their namesakes (Holohan et al., 2013). ABC transporters which are expressed in the PTE include the MDR proteins 2 and 4 (MRP2, *ABCC2* and MRP4, *ABCC4*, respectively), P-gp and BCRP (*ABCG2*), the role of which in renal function has gained momentum in recent years, but has often been overlooked in comprehensive reviews (Brouwer et al., 2015; Nigam, 2015).

3. BCRP, from drug resistance to renal excretion

Since its fortuitous initial description in 1998 by Doyle et al., in a naive MDR human breast cancer cell line (Doyle et al., 1998), BCRP has been implicated in physiological processes way beyond drug-resistance and identified in several cell types and tissues. Different expression levels of BCRP have been reported in the brain and central nervous system, liver, placenta, uterus, mammary glands, prostate, testis, stomach, intestine, colon, lung and the kidney (Huls et al., 2008; Fletcher et al., 2016). This widespread presence in various tissues is indicative of a mechanism of tissue-defense against xenobiotics, and the pool of substrates handled by BCRP confirms this role. Furthermore, the affinity of endogenous substrates such as steroid hormones and small metabolites for BCRP indicates that this transporter may also play a regulatory function. Moreover, a large number of chemotherapeutics and other drugs known to be substrates of both P-gp and MRP are also BCRP substrates (Robey et al., 2009).

Human BCRP is a protein roughly half the size of most members of the ABC superfamily, with 665 amino acids and a molecular mass of 72 KDa, and is encoded by a gene residing on chromosome 4, band 22 (4q22). BCRP and other members of the ABCG family are, in essence, distinct from other prominent ABC transporters such as P-gp and MRPs, which are present in their active assembled forms in the membrane. BCRP is designated a "half-transporter", since it requires two identical monomers to form a functional homodimer. Like all ABC transporters, BCRP is an ATP-driven extrusion pump which transports its substrates from the intracellular space as well as from the lipid bilayer to the extracellular milieu (Shafran et al., 2005; Bram et al., 2009a). BCRP is highly expressed in lactating mammary epithelium where it secretes its substrates into the milk including the vitamin B_2 riboflavin (van Herwaarden et al., 2006; van Herwaarden et al., 2007). This transporter is also highly expressed on the Side Population (SP) of primitive stem cells (Wang et al., 2011). Although its exact function in these cells is still unclear, BCRP likely fulfills a protective function by pumping out toxicants and harmful products of oxidative stress (Doyle et al., 2016).

4. Renal BCRP function, why should we care?

In general, the organic anion transport system constitutes the key mechanism in renal transport and, indisputably, the bulk of

solutes removed via the PTEC is in fact transported into PTEC by OAT1 and OAT3. However, there is another side to renal transport, the one moving substances from PTEC into the lumen, and it is here that BCRP plays its role. Since its functional presence was reported in human PT by Huls et al., in 2008 (Huls et al., 2008), our understanding of BCRP in the kidney has expanded and its active excretory contribution is currently recognized. Basal BCRP expression levels in human PTEC are lower than those of other ABC transporters (*i.e.* P-gp and MRP4), nonetheless, its functional activities are comparable (Caetano-Pinto et al., 2016).

The list of established BCRP substrates is ever increasing. Table 1 lists a number of clinically approved drugs known to be excreted via the renal route that are BCRP substrates. As overlapping substrate specificities among the xenobiotics transporters are apparent, we depicted other renal transporters involved as well. In addition, known drug-drug interactions that result in altered plasma levels of a drug are described. This information was retrieved from the open-access database drug bank (http://www.drugbank.ca/) (Wishart et al., 2006) using a comprehensive search of all approved drugs listed as interacting with BCRP/*ABCG2*, while described to be excreted by the kidney to any given extent. It is evident that a substantial fraction of BCRP transport substrates are chemotherapeutics (25–50%) and also that a considerable substrate specificity overlap exists between BCRP and other members of the ABC superfamily. We identified thirty-two drugs being common transport substrates of BCRP and P-gp, seventeen drugs that share specificities for BCRP and MRP2 and eight drugs that are common substrates for BCRP and MRP4. Given the amount of drugs and drug-interactions observed, it is evident that BCRP, together with its ABC counterparts, does play a prominent role in xenobiotic excretion in PTEC. The importance of these interactions becomes relevant when considering that the wide use of co-medication, combination therapies and concomitant use of different medicines (Conde-Estevez, 2016). This can give rise to an imbalance and interference in renal excretion and consequent systemic accumulation of drugs with unintended consequences.

Beyond its role in drug excretion, BCRP is also implicated in the excretion of a class of endogenous metabolites that particularly reflect kidney function, the so-called uremic solutes (Masereeuw et al., 2014). These solutes are often derived from metabolic processes and, under normal conditions, efficiently excreted by the kidneys. Their systemic retention can be a direct cause of a renal clearance deficit as in acute kidney injury (AKI) or chronic kidney diseases (CKD), or indirectly through competitive interactions at the transporter level as a number of uremic solutes have been identified as substrates (Nigam et al., 2015). Thus far, BCRP has been associated with the handling of several uremic solutes (Mutsaers et al., 2011), including urate, hippuric acid, indoxyl sulfate, kynurenic acid, *p*-cresyl sulfate and *p*-cresyl-glucuronide (Dankers et al., 2013; Mutsaers et al., 2015; Jansen et al., 2016).

4.1. Chemotherapeutic agents influence BCRP activity

Prior to being recognized as a renal transporter, and since its identification, BCRP has held an important place as a major contributor to the chemoresistance of several cancers (Natarajan et al., 2012). The presence of BCRP in multiple tumor types has been correlated with diminished therapeutic outcomes as well as with reduced chemotherapeutic drug retention and efficacy. This is consistent with its tissue protective function under physiological conditions. As highlighted in Table 1, a wealth of anticancer drugs that are BCRP substrates are cleared via the kidneys. In the current review we explore some of the most pronounced effects on BCRP activity by these chemotherapeutic agents, studied in cancer models.

In recent years, the so-called tyrosine kinase inhibitors (TKI) have gained a central role as the frontline treatment in several cancers. By suppressing proliferation-related mechanisms in cancer cells, TKI can be administered in combination with other antitumor agents in order to boost their cytotoxic effects. Imatinib is an example of a TKI that is both a substrate and a modulator of BCRP. It can suppress its expression in BCR-ABL$^+$ cells, a hallmark genetic alteration that enables permanent tyrosine kinase activation, hence conferring upon chronic myelogenous leukemia its aggressive phenotype (Nakanishi et al., 2006). Head and neck carcinomas show particular upregulated kinase activity, and here too imatinib decreased BCRP efflux activity resulting in enhanced doxorubicin cytotoxicity, when combined. In this case, BCRP protein levels were intact, and determined to be inactive in the cytoplasm, a tell-tail sign of post-transcriptional regulation (Chu et al., 2008). Consistently, in MCF-7 tumor spheres exposed to both lapatinib and doxorubicin, BCRP expression was found to be reduced while intracellular accumulation of doxorubicin was enhanced (Chun et al., 2015). Similarly, by inhibiting the epidermal growth factor receptor (EGFR) in lung cancer cells, erlotinib reduced the expression of BCRP in a time-dependent manner. Further, using MDCK-BCRP cells, Pick *et al.,* demonstrated that imatinib and erlotinib can reduce the membrane expression and transport activity of BCRP (Pick and Wiese, 2012). Moreover, an overexpression of ErB2–EGFR2 in MCF-7 cells incresaed BCRP levels and conferred resistance to etoposide, mitoxantrone, 5-fluorouracil, paclitaxel and cisplatin (Zhang et al., 2011). Since their approval, and besides their proven clinical efficacy, TKI have been instrumental to unravel the molecular mechanisms underlying drug resistance, by shedding light on ubiquitous regulatory pathways. A better understanding of the mechanisms of action of this class of drugs and how they affect BCRP activity can improve strategies to tackle BCRP-dependent drug resistance. TKI appear to harbor the potential to influence transport activity not only by directly interacting with BCRP, but also by negatively regulating its expression and function. EGFR/ErB expression is not transversal to all tumors and its expression can significantly vary within the type of cancer and within the patient population; therefore, the clinical impact of TKI-mediated BCRP regulation is still unknown and clear evidence confirming this aspect is currently absent.

BCRP is also known to play an active role in cancer resistance to several conventional anti-cancer drugs. Mimicking cytotoxic bolus drug treatment through 12- to 24-h pulse exposure of ABCG2-silenced leukemia cells, using clinically relevant concentrations of the chemotherapeutic agents daunorubicin and mitoxantrone, resulted in a marked transcriptional up-regulation of ABCG2 (Bram et al., 2009b). Hence, antitumor drug-induced epigenetic reactivation of ABCG2 gene expression in cancer cells appears to be an early molecular event leading to MDR. These findings have important implications for the emergence, clonal selection, and expansion of malignant cells harboring the MDR phenotype during chemotherapy.

The well-known nephrotoxic agent, cisplatin, is widely used in the treatment of a variety of cancers, and nephrotoxicity is often a limiting factor in its use (Oh et al., 2014). Although several transporters are involved in cisplatin handling as a transport substrate, it has been shown *in vitro* that BCRP expression in colon cancer cells can be enhanced by cisplatin exposure (Herraez et al., 2012), demonstrating the inducible nature of BCRP in chemoresistance. In myeloid leukemia clofarabine, cytotoxicity is hampered by BCRP, an effect that is attenuated upon clofarabine phosphorylation by deoxycytidine kinase. The addition of a phosphate group to this drug markedly reduced its affinity for BCRP (Nagai et al., 2011). This coupled force highlights the modulatory effects that enzyme activity can exert on transporter function as well as on tissue specificity of metabolic processes, whereas in tissues lack-

ing this enzyme, BCRP activity towards clofarabine should not be diminished. Taken together, these interactions show that the role of BCRP in chemoresistance is far more advanced than its mere presence in tumors, hence underlining the complexity of the cellular processes involved.

4.2. Regulation of cellular BCRP levels influences renal drug excretion

So far, regulatory mechanisms that are implicated in stress responses, xenobiotic and toxin sensing and cellular homeostasis have been linked to the activation and suppression of functional BCRP activity, as summarized in Fig. 2. Most of the evidence regarding BCRP regulation originates from animal models and tumor-derived cell lines. Arguably, regulatory pathways between humans and rodents may not be conserved, whereas cancer cell lines are transformed and their physiology is altered, and therefore not representative of physiological conditions. Nonetheless, the mechanisms described are ubiquitous and active in several other organs, including the kidneys. Furthermore, many of the drugs that modulate/inhibit such regulatory pathways are transport substrates of BCRP itself (Nakanishi and Ross, 2012), a characteristic that emphasizes the stress-related activation of BCRP upon xenobiotic exposure. The cellular machinery behind the activation, expression and transcription of membrane transporters has been subject of active research, and recently several studies have revealed factors responsible for their regulation.

Diverse studies implicated nuclear factor erythroid-derived 2 (Nrf2), a transcription factor that regulates the expression of stress and inflammation-related genes, in BCRP regulation. In rats, Nrf2 stimulation by sulforaphane induced expression and function of BCRP in brain capillaries, an effect absent in Nrf2-null mice (Wang et al., 2014). In line with these findings, Nrf2 knockdown with siRNA in both prostate and lung cancer cell lines reduced BCRP gene expression and protein levels (Singh et al., 2010). In contrast, Hyuk-Sang Jeong *et al.*, demonstrated that suppression of Kelch-like ECH-associated protein 1 (KEAP1), down-regulated Nrf2, which led to increases in BCRP expression in human renal kidney (HK-2) cells (Jeong et al., 2015). Furthermore, this nuclear factor is also implicated in cancer drug resistance, linked to the activation of metabolic enzymes and enhanced efflux activity in tumors (Bai et al., 2016).

Another transcription factor implicated in modulation of BCRP expression is the ligand-activated aryl hydrocarbon receptor (Ahr), which acts as a sensor of environmental toxins, drugs and other xenobiotics, triggering the expression of metabolizing enzymes (Miller 2015). It was shown that BCRP can be affected by environmental toxins, such as polycyclic aromatic hydrocarbons (PAH), that activate Ahr and upregulate BCRP expression (Hessel et al., 2013). Furthermore, the uremic solute *p*-cresyl glucuronide can functionally induce BCRP through a yet unknown mechanism (Mutsaers et al., 2015). In terms of endogenous factors, steroid hormones such as progesterone and estradiol have been described to downregulate BCRP (Dankers et al., 2012). In isolated rat and mouse brain capillaries exposure to 17-estradiol (E2) reduced the expression and efflux activity of BCRP, and furthermore, E2 decreased the activity of a-serine-threonine protein kinase (Akt) as well as phosphoinositide 3-kinase (PI3K) (Hartz et al., 2010).

The role of protein kinase activity has also been associated with modulation of BCRP expression and activity, particularly in drug-resistance studies, where the inhibition of the PI3K/Akt signaling pathway by LY294002 reduced BCRP expression and function in both MCF-7 and MDCK-BCRP cells (Komeili-Movahhed et al., 2015). Furthermore, PI3K/Akt inhibition blocked the targeting of BCRP to extracellular vesicles, hence overcoming MDR in breast cancer cells (Goler-Baron et al., 2012). The use of gefitinib, a TKI used as a chemotherapeutic agent, decreased BCRP expression and activity in advanced non-small lung cancer patient cells (Galetti et al., 2015). Further studies have confirmed the role of tyrosine kinase-dependent signaling in BCRP regulation. Downstream inhibition of the constitutive EGFR pathway downregulated BCRP expression *in vitro* (Pick and Wiese, 2012), implicating Akt activity in BCRP gene expression. Other factors such as the peroxisome proliferator-activated receptor α (PPARα), a steroid hormone receptor that mediates lipid homeostasis, was shown to increase BCRP efflux activity in human cerebral microvascular endothelial cells – hCMEC/D3 (Hoque et al., 2015). The pro-inflammatory cytokines interleukin 1-β and 6 (IL-1β and IL-6, respectively) together with the tumor necrosis factor α (TNF-α) can also reduce the expression an activity of BCRP in these cells (Poller et al., 2010).

Plasma membrane components, such as lipids and cholesterol, have been linked to the post-transactional regulation of BCRP. This suggests that BCRP is sensitive to the lipid nature of its surroundings (Hegedus et al., 2015) as is its MDR efflux transporter counterpart, P-gp (Assaraf and Borgnia, 1994; Drori et al., 1995; Borgnia et al., 1996). Further evidence implicating lipids in regulation of BCRP activity emerges from clinical studies, where patients with familial hypercholesterolemia undergoing statin therapy showed reduced BCRP expression and transport activity (Hu et al., 2011). Pharmacokinetics studies have correlated the *ABCG2* 421C>A polymorphism with increased low-density lipoprotein cholesterol in response to rosuvastatin, a BCRP transport substrate, suggesting that cellular BCRP regulation can be influenced by its own substrate (Hu et al., 2011). *In vitro* cholesterol membrane content was shown to have a significant impact on BCRP activity, where cholesterol loading has a positive impact on transport activity, and sterol-sensing motifs have been identified in the BCRP structure (Pal et al., 2007). Furthermore, *ex vivo* cholesterol depletion was also shown to decrease BCRP expression and activity (Hu et al., 2011).

In a chronic kidney disease model, where 5/6 nephrectomy was performed in male rats, renal BCRP expression decreased and correlated with both injury severity and cytokine increase, an effect that is absent in female rats (Lu and Klaassen, 2008). This initial evidence suggested a prominent role for BCRP in kidney disease. Adding to the complexity of BCRP regulation, a study by Martín et al., showed that increased melatonin levels lead to BCRP promoter methylation and subsequent silencing of the BCRP gene and the function of its gene product. Moreover, the epigenetic alterations that occur in cancer cells may well be a hallmark in the development of transporter-mediated MDR (Arrigoni et al., 2016). Another aspect of BCRP regulation is related to the fact that the pathways now implicated in its activity are also responsible for the regulation of other ABC transporters that are co-expressed along with BCRP in numerous tissues (Miller, 2015). These findings strongly suggest that members of the ABC superfamily that share similar substrates, and therefore similar functions, may also share the same regulatory pathways. This holds true in the blood brain barrier where BCRP and P-gp activation have common denominators, such as cytokines, Ahr and Nrf2 (Miller, 2015), and in tumor cell lines where TKI also inhibit both ABC transporters. Furthermore, the mechanisms promoting upregulation of BCRP may well be independent, where different stimuli led to the same result, either initiated by an exogenous source, like a toxicant triggering Ahr or by a more intrinsic mechanism, like cytokines which activate the PI3K/Akt pathway (Fig. 2). The clinical implications of these cellular regulatory mechanisms, not only implicating BCRP, and how they can govern the renal clearance of drugs, is in large part yet to be resolved. EGFR signaling plays a considerable role in maintaining physiological processes, and despite the fact that current TKI seem to lack a nephrotoxic potential often observed with conventional chemotherapeutics (Cosmai et al., 2015), little if any clinical evidence exists concerning the effects of combination therapies in drug disposition and nephrotoxicity, where several drugs are BCRP

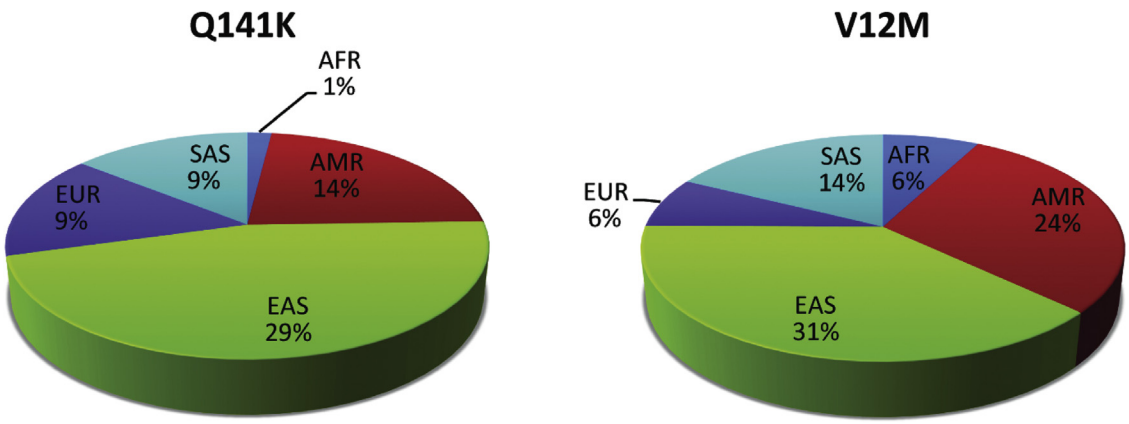

Fig. 3. Distribution of the ABCG2 Q141K and V12M variant alleles in five super-populations. EUR: European, SAS: South Asian, AFR: African, AMR: Ad Mixed American, EAS: East Asian.

transport substrates. This illustrates where both renal and cancer research can overlap and highlights the need for novel and concise research that takes into account the complexity of the mechanisms underlying pharmacological drug interactions in the kidney.

5. The pharmacogenomics profile alters BCRP-mediated transport

As many drugs compete for similar binding sites of transporters, drug-drug interactions might occur upon co-administration. Consequently, drug concentrations will necessarily rise, thereby leading to a nephrotoxic event (Emami Riedmaier et al., 2012; Crean et al., 2015; Wilmer et al., 2016). In addition, the administration of a compound with an intrinsic toxicity, like the antibiotic gentamicin or the immunosuppressive drug cyclosporine A, may directly result in drug-induced kidney injury (de Arriba et al., 2013). These effects may be more pronounced in patients with genetic variants of BCRP, as described for uric acid. The role of pharmacogenomics has become evident over the past years and emerges as relevant for predicting the safety and efficacy of therapies (Awdishu and Joy, 2016) as well as for personalized medicine (De Mattia et al., 2015; Gillis and McLeod, 2016). To date, over 60 SNPs have been characterized in the coding region of BCRP, both missense and nonsense variants, of which two SNPs including Q141K and V12M, display a relatively high allele frequency of 12% and 16% in the global population, respectively. Interestingly, the frequency is distributed among the five known super-populations (Fig. 3). Both variants are most abundantly present in the East Asian population with a frequency of about 30% for both polymorphisms. In addition to disturbed xenobiotic handling, there is a clear genome-wide association between BCRP-Q141K and gout manifestation. Gout is characterized by elevated plasma urate levels which consequently lead to the formation of crystals within joints (Dehghan et al., 2008; Woodward et al., 2009; Yang et al., 2010; Ichida et al., 2012). Urate is derived from purine nucleotide catabolism following dietary intake and endogenous biosynthesis of purine nucleotides. In healthy subjects, urate is cleared by the gastrointestinal tract for approximately one-third, whereas two-thirds are secreted via the kidneys by glomerular filtration and active tubular secretion involving BCRP (Choi et al., 2005; Dankers et al., 2013). The Q141K variant contributes to the development of hyperuricemia as the clearance into the pro-urine is impaired (Ichida et al., 2012), leading to increased plasma urate levels and onset of gout. Next to the Q141K variant, the Q126X variant has also been associated with gout (Matsuo et al., 2013), although this variant is less common as it has an average allele frequency of only 0.1% in the general population. Next to gout, elevated urate levels have been associated with the progression of CKD (Duranton et al., 2012; Dankers et al., 2013). Dankers *et al.*, showed that uric acid inhibited BCRP-mediated transport in a competitive manner *in vitro*. Moreover, in hyperuremic mice, levels of L-kynurenine and kynurenic acid, both of which are metabolites of tryptophan metabolism, were retained in plasma. These metabolites are known substrates for BCRP and their elimination is hampered by elevated uric acid levels through competition with the same efflux transporter (Mutsaers et al., 2011; Dankers et al., 2013; Jansen et al., 2016). Elevated levels of uric acid, L-kynurenine and kynurenic acid are known to exert deleterious effects on many biological systems within the body, e.g. on vasculature endothelial cells (Duranton et al., 2012). As BCRP is known to mediate transport of multiple uremic toxins, as previously described (Mutsaers et al., 2011; Jansen et al., 2016), hyperuricemia might have a significant impact on the removal of these metabolites and therefore will contribute to the pathology of CKD.

The Q141K genotype is also linked to altered BCRP function in terms of pharmacokinetics, consequently influencing xenobiotic disposition beyond urate (Noguchi et al., 2014). For example, the plasma levels of the TKI sunitinib were found to be significantly higher in human renal cell carcinoma patients with a homo- and heterozygous genotype as compared to wild type BCRP (Mizuno et al., 2012; Miura et al., 2014). Consistently, in *abcg2*$^{-/-}$ knockout mice the values of sunitinib C_{max} were found to be significantly higher when compared to wild type mice (Mizuno et al., 2012). Furthermore, elevated plasma levels of the topoisomerase I inhibitor diflomotecan were found in heterozygous Q141K patients (Sparreboom et al., 2004). This may also account for numerous other anticancer agents resulting in elevated drug plasma levels and increased toxicity risk to various organs including the kidney (Noguchi et al., 2014). Nevertheless, this is not observed for all drugs, as the antifolate methotrexate, which is predominantly cleared by the kidneys and associated with intrinsic renal toxicity (Kumar and Shirali, 2014), did not exhibit an altered pharmacokinetics profile in Q141K variants (Yanagimachi et al., 2013). The BCRP-R482G and -R482T variants, on the other hand, may result in altered methotrexate pharmacokinetics as suggested by *in vitro* studies using Human Embryonic Kidney (HEK)-293 cells overexpressing these transporter variants (Chen et al., 2003; Shafran et al., 2005). Molecular pharmacological studies demonstrated that this may be caused by reduced substrate transport and ATP turnover but most likely not due to changes in substrate binding *per se* (Ejendal et al., 2006). Interestingly, recent studies showed the complex role of various BCRP residues on impaired drug export function via

processes like altered posttranslational modifications, attenuated protein trafficking towards the plasma membrane and alterations in the drug binding site *in vitro* (Haider et al., 2015). However, many of these residues, like BCRP-R482, have a very low prevalence in the population and are not yet identified in altered clinical pharmacokinetics.

The BCRP-Q141K variant transporter is also associated with reduced transport of the antidiabetic drug of the sulfonylureas class, glyburide, hence influencing diabetic treatment (Pollex et al., 2010). Both the apparent transport K_t and V_{max} values of glyburide were significantly higher in the Q141K variant as compared to the wild type BCRP. Concurrently, the exact molecular mechanism underlying BCRP-Q141K dysfunction remains elusive as some studies showed a similar plasma membrane expression of BCRP of the wild type and mutant transporters (Zamber et al., 2003; Morisaki et al., 2005), whereas others detected reduced expression levels of BCRP (Imai et al., 2002; Kondo et al., 2004). In addition, a decreased ATPase activity has been detected in Q141K BCRP mutants which might explain the less efficient BCRP-mediated glyburide export (Mizuarai et al., 2004; Morisaki et al., 2005).

To date, the knowledge on the effects of BCRP-V12M on (renal) pharmacokinetics are less pronounced and more controversial (Noguchi et al., 2014). As shown by Imai *et al., in vitro*, the transport function of BCRP-V12M was not impaired as compared to wild type BCRP as determined by topotecan accumulation, a known anticancer drug substrate of BCRP (Imai et al., 2002). In contrast, Mizuarai et al., showed that BCRP-V12M cells were more sensitive to topotecan treatment due to the accumulation of this cytotoxic compound (Mizuarai et al., 2004). These discrepancies might be related to the different species origin of cells applied in these studies. Mizuarai et al., used BCRP-transfected porcine renal cells (LLC-PK1) for functional testing, whereas Imai *et al.,* performed functional experiments in mouse fibroblast cells (PA317). BCRP physiology might vary fundamentally among cell models in terms of processing from gene to protein to function, and this might explain the different study outcomes (Jansen et al., 2014). A more reliable approach would be to perform CRISPR-Cas gene editing to introduce polymorphisms in human renal epithelial cell models which constitute an endogenous BCRP expression system (Jansen et al., 2014; Freedman et al., 2015). This would allow to study the effect of BCRP-V12M on BCRP function in a more physiologically relevant manner.

Interestingly, the V12M SNP has been associated with alternative splicing of BCRP exon 2 in liver cells from human Hispanic origin and reduced BCRP liver expression was detected (Poonkuzhali et al., 2008), potentially pointing towards alterations in drug disposition in these subjects. However, the impact on the functional level remains elusive as Chinese acute leukemia patients harboring the wild type BCRP genotype, display a longer disease-free survival and overall a decreased mortality as compared to BCRP hetero- or homozygous leukemia patients (Wang et al., 2011). BCRP mRNA expression levels in these patients were solely detected in peripheral blood cells. It would have been of interest to investigate renal BCRP mRNA expression in this population, as this could further elucidate the possible role of the V12M polymorphism in the kidney. Nonetheless, a full picture of the role of this BCRP polymorphism in drug clearance could be more complete with the protein's renal expression levels.

6. Sex, species and gender differences influence BCRP function

BCRP expression has been shown to be sex and species-specific, which is in part related to the fact that its expression is regulated by hormones like estradiol and testosterone (Tanaka et al., 2005). As such, humans often respond differently to drugs than predicted from preclinical data obtained in animal studies because the pharmacokinetics and pharmacodynamics profiles are distinct (Soldin and Mattison, 2009). Focusing on differences in renal BCRP expression in rodents, Dankers et al., showed that BCRP gene expression in kidneys isolated from female Friend Leukemia virus B strain (FVB) mice was significantly lower as compared to male FVB mice (Dankers et al., 2012). Consistently, in a study performed by Tanaka et al., renal BCRP expression in female C57BL/6J mice tended to be lower as compared to male mice, though not statistically significant (Tanaka et al., 2005). In the same study, Sprague-Dawley female rats showed significantly less BCRP gene expression as compared to male rats. Interestingly, renal BCRP expression in female rats was found to be significantly lower as compared to female C57BL/6J mice (Tanaka et al., 2005). In general, it is well accepted that female animals display a lower renal BCRP expression than males, most likely due to the suppressive effect of estradiol as compared to males in which testosterone has an inductive effect, though clear interspecies differences are observed between sexes (Martin et al., 2013; Gal et al., 2015). In translation to humans, Huls *et al.,* showed that kidneys of male FVB mice and rats (strain not reported, but communicated to be Wistar Hanover) exhibited a much higher renal BCRP gene and protein expression as compared to human kidneys (Huls et al., 2008). These data emphasize that translating animal pharmacokinetics data to human requires caution, particularly when interpreting BCRP transport substrates. This observation is in line with the finding that many drugs fail in clinical studies due to adverse toxic effects, simply explained by the inaccuracy of animal models to reflect the genuine pharmacokinetics profile in humans (Guengerich, 2011). In addition, significant differences in postnatal nephron development and maturation may exist between sexes, as well as between species. The ontogeny of drug transporters in the kidney was recently reviewed (Brouwer et al., 2015), however, the amount of information available is scarce, in particular for human. Allegaert et al. (Allegaert et al., 2007) demonstrated that the renal excretion of drugs is commonly slow in neonates and dominated by glomerular filtration, which is in line with postnatal development and the harmful effects that drugs can have when used during pregnancy and in preterm-born infants, leading to renal mal-development and congenital anomalies of the kidney and urinary tract (Schreuder et al., 2011).

Importantly, next to sex, gender differences have been also shown to influence preclinical studies (Klein et al., 2015). Gender is characterized by the socio-cultural environment that influences biology. For example it has been shown that housing animals in groups instead of single animals affects data variability (Prendergast et al., 2014). Moreover, researcher gender is associated with handling and attitude towards male and female animals (Klein et al., 2015). As such, animals handled by male researchers demonstrated higher stress levels as compared to animals treated by female scientists (Sorge et al., 2014). Interestingly, this researcher gender effect can be translated to BCRP function as induced stress levels can influence plasma testosterone levels (Sabolic et al., 2007; Mahmoud et al., 2016; Ullah et al., 2016). Subsequently, this could potentially alter renal BCRP expression and function as testosterone is known to regulate BCRP (Tanaka et al., 2005; Dankers et al., 2012).

Thus far, these compelling findings lack validation/translation at the clinical setting. It is well established that renal and malignant disease incidence and prevalence can vary greatly with age and gender. Survival rates for female patients undergoing dialysis are lower (Hecking et al., 2014) and overall cancer mortality is higher among males (Cook et al., 2011). Nonetheless, our understanding of the role played by gender differences in transport activity in disease and drug treatments, remains insufficient.

7. Conclusions and future perspectives

A substantial fraction of anticancer drugs cleared by the kidneys are BCRP substrates. Despite its functional presence in the kidney, little is known about the impact of renal disease on the disposition of such drugs (Lameire et al., 2016; Wong et al., 2016). On the other hand, renal function is a major concern in chemotherapy. For example, for cisplatin, an integral frontline treatment component in several of the most common malignancies, nephrotoxicity is often a dose-limiting factor. Moreover, most cancer patients fall in the age group at risk of kidney disease. For safer therapy, a better understanding of both nephrotoxic mechanisms and kidney disease in cancer chemotherapy is warranted. In depth knowledge on the limitations of the renal function of cancer patients can contribute to better design chemotherapeutic drug regimens. Furthermore, the impact of antitumor agents on the renal contribution of BCRP is largely unknown. The same regulatory mechanisms governing drug resistance induced by drugs such as TKIs, namely imatinib, lapatinib and erlotinib, are also present in the kidneys. Despite studies reporting the relative safety of TKI's with respect to nephrotoxicity (Cosmai et al., 2015), virtually nothing is known on how these modulatory drugs may affect renal excretion.

AKI and CKD are a global health problem with significant morbidity and mortality, which affects 5–7% of the world population. The number of these patients continues to rise as a consequence of the increasing incidence of diabetes mellitus, the prevalence of insufficiently treated hypertension, and the aging population with its related progressive decline in renal function (Jha et al., 2013; Leung et al., 2013). The total medical care expenditure for CKD was nearly $58 billion in 2012 (U.S. Renal Data System, 2013). For both social and economic reasons, optimizing resources and developing novel strategies to tackle kidney disease is imperative.

Genetic factors, such as polymorphisms and differences between species, with respect to BCRP distribution and expression are recognized as important variables when it comes to drug absorption and distribution. On the other hand, the influence of sex and in particular gender is often neglected. As such, raising awareness for the importance of sex and gender as a biological variable in biomedical research is key for future success of translational medicine.

The advent of personalized medicine holds the potential to both elucidating the mechanisms underlying drug resistance as well as improving the clinical outcomes of cancer treatment (Li et al., 2016). The meta-data obtained by various "Omics" analyses can simultaneously provide information about genetic variants expression, cellular pathway activation, transporter expression and, together with the knowledge on drugs handled by BCRP as described in this manuscript, could significantly improve patient survival, with BCRP as a therapeutic target. However, this approach is still limited to pre-clinical setups, whereas clinical trials making a slow debut into clinical practice must be enhanced and accelerated. On the other hand, knowledge on renal abundance of BCRP in humans is emerging, as recently reported using quantitative proteomics (Fallon et al., 2016), and new approaches quantifying renal transporters distributed both at apical and basolateral membranes (Uchida et al., 2016). Hence, the role of BCRP in renal drug excretion is becoming increasingly acknowledged.

Nephropharmacology is the discipline that studies the connection between clinical pharmacology and nephrology (Atkinson and Huang, 2009). A better understanding of the role of drug transporters and their regulation in the kidney will aid in the development of safe drug therapies. The relevance of BCRP in the disposition of clinically relevant drugs in addition to its established role in chemoresistance, is now widely recognized by key regulatory bodies including the US Food and Drug Administration (FDA). Their guidelines include BCRP testing for relevant drug interactions studies (International Transporter et al., 2010). Several reports, including those from the International Transporter Consortium (ITC) – http://www.ascpt.org – have identified BCRP as a prominent player in drug-interactions in the intestine, liver and blood-brain barrier, in both adult and developing human organs (Brouwer et al., 2015; Mao and Unadkat, 2015). We here strongly advocate the inclusion of BCRP in studying drug interactions at the level of the kidney. Towards this end, innovative, humanized, preclinical models that aid in drug screening during development and reliably predict drug disposition and clinical performance are needed. Recent approaches in renal cell biology focus on the generation of 3-dimensional cell culture models due to the more advanced features that these models offer by being more closely related to physiological conditions (Sanchez-Romero et al., 2016). This can even be enhanced with the implementation of flow in the culture conditions. Furthermore, down-scaling the size with microfluidics towards a so-called 'kidney-on-a-chip' using human or patient-derived cells has great potential for drug screening (Wilmer et al., 2016). In addition, stem cell-derived kidney organoids have been developed to understand kidney regeneration but also to present a platform that can be used for drug screening and disease modeling (Sachs and Clevers, 2014; Chuah and Zink, 2016; Schutgens et al., 2016). Drug development may be advanced further with humanized animal models, such as the humanized BCRP mouse in which the rodent transporter is replaced by its human orthologue (Dallas et al., 2016). Finally, results of these biomedical innovations could be implemented in mechanistic models that mathematically describe underlying processes implicated in renal drug handling (Scotcher et al., 2016).

In conclusion, we herein propose to recognize the importance of BCRP in chemoresistance and renal excretion for effective cancer treatment and, concomitantly, preserve kidney function.

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