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REVIEW

Revisiting strategies to target ABC transporter-mediated drug resistance in CNS cancer

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ABSTRACT A significant number of anticancer drugs fail to treat primary and metastatic brain tumors primarily because of the complex blood-brain barrier (BBB) and overexpression of ATP-binding cassette (ABC) transporters, which decrease drug penetration into the central nervous system and ultimately into tumors. It is noteworthy that the ABC transporters, ABCB1 [known as P-glycoprotein (P-gp)] and ABCG2 [known as breast cancer resistance protein (BCRP)], are overexpressed in brain tumors, including common gliomas. The co-presence of these transporters may negate the inhibition of either transporter, particularly if both transport the same anticancer drug. The cellular export of drugs by ABC transporters has been implicated in mediating resistance to anticancer drugs. However, the clinical relevance as a therapeutic target in human tumors remains a matter of contention. Although effective and clinically approved ABC transporter inhibitors could potentially overcome drug resistance, none are currently approved. Furthermore, the ABC transporter inhibitors in clinical trials produced low or no clinical efficacy, significant toxicities, and unsuitable pharmacokinetic profiles. Therefore, innovative approaches are needed to efficaciously and simultaneously inhibit these transporters to surmount anticancer drug resistance. This review emphasizes the clinical significance of ABC transporters in diminishing the efficacy of brain tumor treatments. The molecular alterations in BBB following brain tumor development, which are linked to various cancer therapies, are discussed. The overexpression of ABCB1 and ABCG2 at the BBB is discussed, potential strategies to decrease the export of chemotherapeutics by these transporters and the associated challenges and failures are discussed, and the implementation of novel approaches is considered.

KEYWORDS ABC transporters; MDR; ABCG2; ABCB1; Brain Tumors; BBB

Introduction

ATP-binding cassette (ABC) transporters are among the most diverse protein superfamilies in humans[1,2]. These ABC transporters are structurally unique, ATP-dependent, and efflux a wide range of biomolecules and xenobiotic compounds across cellular membranes inside or outside of cells[3]. The ABC structure consists of four core domains, including two transmembrane domains (TMDs) embedded within the membrane bilayer and two ABC domains [or nucleotide binding domains (NBDs)] within the cytoplasm[4,5]. The ABC transporter superfamily has a distinct sequence level that is characterized by a common set of highly conserved motifs in the ABC domains[6]. In contrast, the TMDs of ABC transporters have a wide range of sequences and topologies, reflecting the chemical diversity of the translocated substrates. Thus, the diversity in the transported substrates is

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determined by multiple alpha-helices (typically 6) forming each TMD. These helices merge into two TMDs to form the translocation channels, which allow the substrate to pass across the membrane. The helices have diverse sizes, conformations, and chemical properties, depending on the transporter. Consequently, the substrates of the transporters include ions, sugars, peptides, lipids, and drugs[7].

Different ABC transporter subtypes are located on the membranes of cells in various organs, including the brush border membrane of enterocytes, the biliary canalicular membrane of hepatocytes, the luminal membrane in the proximal tubules of the kidney, and epithelial cells at the blood-brain barrier (BBB)[8]. Numerous studies have reported that ABC transporters have a significant role in drug absorption, distribution, and elimination[3]. Currently, at least 50 members of the human ABC transporter family have been identified that can be classified into seven subfamilies (ABCA, ABCB, ABCC, ABCD, ABCE, ABCF, and ABCG) based on structural similarity[9,10].

ABC transporters are involved in many transport functions. Substrates that are transported by ABC transporters include lipids, peptides, amino acids, carbohydrates, vitamins, ions, glucuronide and glutathione conjugates, and xenobiotics[1,11,12]. Some ABC transporters are involved in regulating the level of specific endogenous biomolecules, whereas most ABC transporters are primarily involved in transporting xenobiotics from cells that ultimately are excreted from the body[13]. Dysfunctional ABC transporters due to genetic mutations produce a wide range of metabolic disorders, including Tangier's disease, Stargardt's disease, and adrenoleukodystrophy, that result in the excessive accumulation of endogenous or exogenous substances[13-15]. **Table 1** shows the anticancer drugs that are transported by ABC transporters.

ABC transporters can be classified as importers and exporters, based on their primary function[27]. ABC transporters can mediate substrate influx and efflux and remove intracellular toxins and drugs in prokaryotes[28]. There are different members of the ABC transporter family in prokaryotes. These transporters have different names, mechanisms, and functions that are different from eukaryotes. For example, importer transporters [MalEFGK2 (maltose) and BtuCDF (vitamin B12)][29] have been reported. However, exporter transporters [MacAB-TolC

Table 1 Classes of anti-cancer drugs (substrates) transported by ABC transporters

Transporter gene name	Transporter protein name	Substrate class	Anti-cancer agents (substrates)
ATP Binding Cassette Subfamily B Member 1 (ABCB1)[16-20]	P-glycoprotein 1 (P-gp)	Neutral and cationic hydrophobic	Alkylating agents: temozolomide (TMZ), procarbazine, and carmustin Tyrosine kinase inhibitors: erlotinib, dasatinib, sunitinib, and sorafenib Anti-microtubule taxanes: paclitaxel and docetaxel Topoisomerase inhibitors: topotecan, doxorubicin, daunorubicin, and mitoxantrone Vinca alkaloids: vinblastine and vincristine PARP1/2 inhibitor: veliparib (ABT-888) MGMT inhibitor: lomeguatrib Epipodophyllotoxins
ATP Binding Cassette Subfamily G Member 2 (ABCG2)[21-23]	Breast Cancer Resistance Protein (BCRP)	Partial overlap with ABCB1 and ABCC1	Nucleoside analogs: cytarabine Tyrosine kinase inhibitors: erlotinib, dasatinib, sunitinib, sorafenib, and nilotinib Anthracyclines: doxorubicin, mitoxantrone, and daunorubicin Topoisomerase inhibitors: mitoxantrone, irinotecan, SN-38, and doxorubicin Dihydrofolate reductase inhibitor: methotrexate (MTX)
ATP Binding Cassette Subfamily C Member 1 (ABCC1)[24-26]	Multidrug resistance-associated protein 1 (MRP1)	Anionic lipophilic overlap specificity with ABCB1 and ABCG2	Alkylating agents: cyclophosphamide Topoisomerase inhibitors: doxorubicin, etoposide, camptothecin, and irinotecan Anti-microtubule taxanes: paclitaxel Dihydrofolate reductase inhibitor: methotrexate Vinca alkaloids: vinblastine and vincristine Alkylating agents: cisplatin Antimetabolites Dihydrofolate reductase inhibitor: methotrexate (MTX)

and HlyB-HlyD] have also been identified[30,31]. The prokaryotic importers require a substrate-binding protein to deliver the substrate to the channel, whereas eukaryotic transporters act directly because the substrate has access to the transporter in the absence of a substrate binding protein. Furthermore, prokaryotic transporters are mainly located on the plasma membrane, whereas eukaryotic transporters can be located on the plasma membrane and intracellular organelles. In eukaryotes, the ABC transporters function primarily as efflux proteins that extrude toxins and xenobiotics out of cells[28].

The ABCB1, ABCG2, and ABCC2 transporters are localized on the luminal side of brain capillary endothelial cells in the BBB and transport endogenous and exogenous compounds into the brain[32,33]. Other ABC transporters, such as ABCC1, ABCC3, ABCC5, and ABCC6, are localized on the basolateral side of brain capillary endothelial cells of the BBB (**Table 2**)[38,39]. Study findings involving the expression and distribution of ABCC transporters at the BBB are equivocal[40] but it has been suggested that the ABCC1, ABCC2, and ABCC3 transporters are primarily localized on the luminal membrane of capillary endothelial cells[39]. The localization of ABC transporters at the luminal and/or basolateral membranes of the BBB may indicate potential roles in regulating the influx and efflux of molecules, such as nutrients, waste metabolites, toxins, xenobiotics, and small peptides[19].

The ABC transporter orientation is regulated by changing the conformation of TMDs, which allows the transporter to have an inward- or outward-facing orientation. Binding of the transport substrate and Mg-ATP, followed by ATP hydrolysis and product release, produces conformational flipping of the membrane domain for alternate access between inward and outward[41]. The three models of ABC transporter mechanisms are: alternating site, switch, and constant contact, which are based on structural and biochemical data[41]. Although there are some fundamental elements that these models have in common, such as ATP-dependent NBD dimerization and flipping of the TMD between an outward- and an inward-facing conformation, the models differ in their underlying functional mechanism[41]. In addition to these classical mechanisms associated with ABC transporters, novel mechanisms have been identified. For example, Bi et al.[42] discovered a processive O antigen translocation mechanism in Gram-negative bacteria, in which the transport of O antigens to the periplasm is mediated by an ABC transporter *via* the capsule polysaccharide export inner membrane protein (Wzm) and the Wtz1 domain at the C terminus of the O-antigen export protein[42]. Based on structural-based analysis, Qian et al.[43] suggested that the ABCA1 transporter mediates the export of phospholipids and cholesterol to extracellular apolipoprotein A-1 to produce high-density lipoprotein (HDL) by a "lateral access" or lipid flopping model, not by the conventional alternate access mechanism.

Overexpression of the ABC transporters in cancer cells is one of the major mechanisms that produces multi-drug resistance (MDR) in tumors, which significantly decreases or abrogates anti-cancer drug efficacy[44] (this topic will be discussed in more detail later in this review).

ABC transporter family members and brain function

The BBB is a neurovascular unit (NVU) composed of brain capillary endothelial cells, pericytes, astrocytes, and the basal lamina[45]. The endothelial cells are located on the innermost portion of the BBB and separate blood from brain tissue.

Table 2 ABC transporters in brain capillary endothelial cells

Transporter gene name	Transporter protein name	Importer/exporter	Luminal/basolateral expression	Tissue expression	Ref.
ABCB1	P-glycoprotein (P-gp)	Exporter	Luminal	Brain capillary endothelial cells	34
ATP-Binding Cassette Sub-Family G Member 2 (ABCG2)	Breast Cancer Resistance Protein (BCRP)	Exporter	Luminal	Brain capillary endothelial cells	34,35
ATP-Binding Cassette Sub-Family C Member 1 (ABCC1)	Multidrug Resistance-associated Protein 1 (MRP1)	Exporter	Luminal and Basolateral	Brain capillary endothelial cells	35,36
ATP-Binding Cassette Sub-Family C Member 4 (ABCC4)	Multidrug Resistance-associated Protein 4 (MRP4)	Exporter	Luminal and Basolateral	Brain capillary endothelial cells	35
ATP-Binding Cassette Sub-Family B Member 5 (ABCC5)	ABCC5	Exporter	Luminal	Brain capillary endothelial cells	37

The endothelial cells are the primary cellular structures of blood capillaries[46]. Capillaries in the CNS lack fenestrations and are connected by tight junctions, which limit the paracellular diffusion of drugs into the brain[47]. This feature differs from peripheral capillaries, where many biological and xenobiotic molecules can cross endothelial barriers *via* paracellular diffusion[48]. The endothelium of the BBB is formed by close contact with astrocytes and/or pericytes and is mediated in part by differences in cell adhesion molecules between central and peripheral cells[49]. Astrocytes and pericytes support membrane integrity, stability, and homeostasis[45].

The presence of ABC transporters in the BBB (primarily ABCB1 and ABCG2), which actively efflux compounds[49], provides another mechanism that protects neurons from toxic molecules (**Figure 1**). The ABC transporters in the brain are located on astrocytes, neurons, and microglia and are an important component of the BBB[50]. Several cellular and extracellular factors can alter the expression of ABC transporters at the BBB, including diet, inflammatory and oxidative stress, toxicant exposure, and pharmacotherapy[51]. For example, *in vivo* studies involving rats and mice indicated that liver failure significantly alters the expression and function of ABC transporters at the BBB, which alters the efficacy and toxicity of some drugs[39]. The function of ABC transporters is also affected based on the location in the BBB and transporter-specific maturation. For example, the expression of ABCB1 is low near the time of birth but increases with age in human brain cortical tissue[52]. Several drugs or environmental toxins can affect ABC transporter expression or function (the details of many of these effects are discussed in subsequent sections of this review that focus on the functions of specific ABC transporter subtypes).

The ABCB1 and ABCG2 transporters are present in the luminal membrane of brain capillary endothelial cells and restrict the entry of dual ABCB1/ABCG2 substrate drugs into the brain[17,22,53,54]. Consequently, ABCB1 and ABCG2 transporters have a major role in protecting neural cells from endogenous or exogenous toxins[55]. High levels of ABCB1 and ABCG2 mRNA are present in brain blood vessels[17]. The majority of anticancer drugs targeting specific biomolecules

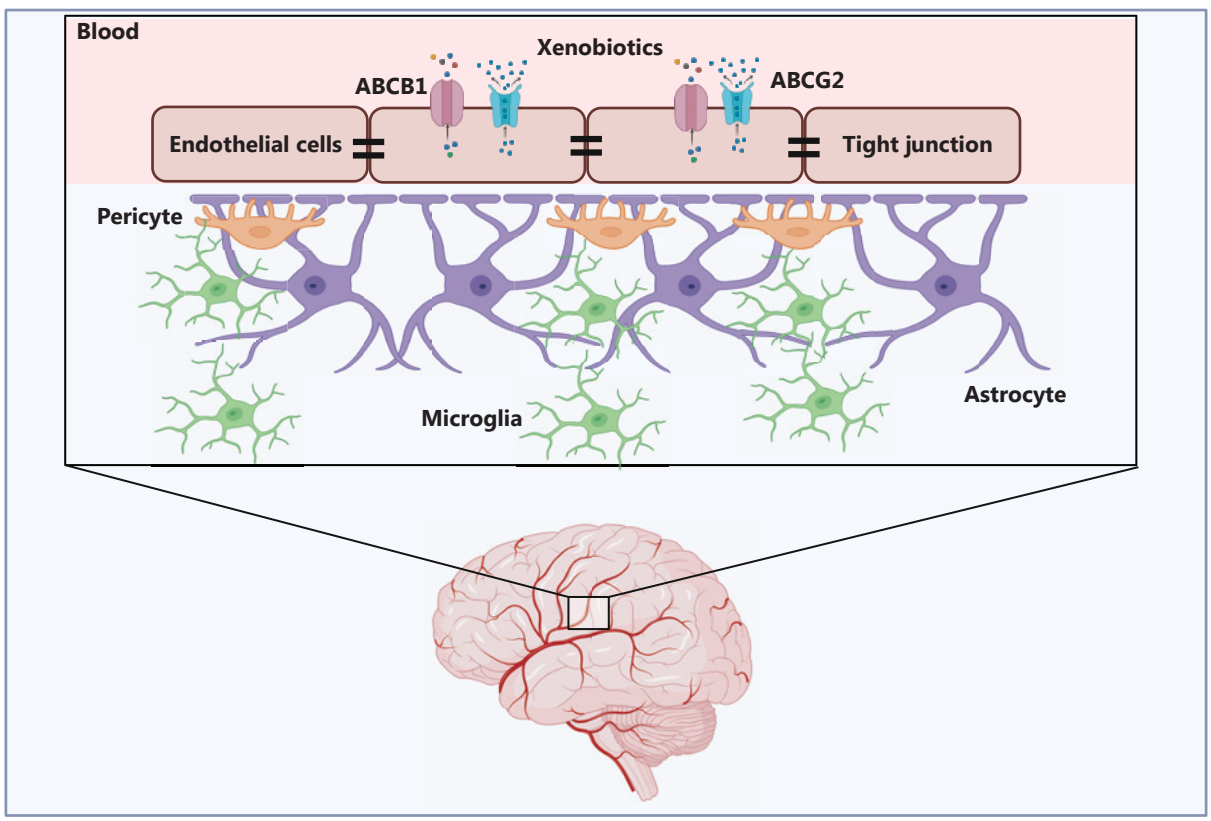


Figure 1 The role of the ABC transporters (ABCB1 and ABCG2) in the blood-brain barrier (BBB). The ABC transporters are located primarily on endothelial cells. The transporters have limited expression on astrocytes, pericytes, and microglia. The ABCB1 and ABCG2 transporters are important components of the BBB, where ABCB1 and ABCG2 actively efflux endogenous and xenobiotic molecules.

that have been approved for clinical use are ABCB1/ABCG2 substrates, which can significantly decrease efficacy[22,54]. Numerous studies have shown that the ABCB1 and ABCG2 transporters are overexpressed in the membranes of brain tumor cells, thus posing a second barrier to the efficacious treatment of brain tumors[56-58].

ABCB1 structure and efflux function

ABCB1 has two TMDs and two NBDs in a single polypeptide chain and six transmembrane α-helices in each of two homologous halves. The TMDs are essential by forming a central hydrophobic cavity in the drug-binding site. The two NBDs bind and hydrolyze ATP and are situated in the cytoplasmic area. The C-loop and conserved motifs (Walker A and Walker B), which are necessary for ATP binding and hydrolysis, are found in these domains[59]. The wide and flexible binding pocket of ABCB1 can bind hydrophobic and amphipathic substrates with a variety of structural variations[60]. Thus, the efflux of a variety of chemotherapeutic drugs, including vincristine, paclitaxel, and doxorubicin, occurs simultaneously at several binding sites[61]. ABCB1 switches between conformations that face outward (substrate-release) and inward (substrate-binding) during the transport driven by ATP binding and hydrolysis, as mentioned above with other ABC transporters. These structural features allow the drugs that are hydrophobic to permeate the lipid bilayer and attach to the transmembrane cavity inward-facing binding site. NBDs undergo a conformational shift to the outward-facing configuration after ATP molecule binding. The substrate is then released into the extracellular space because of the change in binding affinity. Finally, ATP hydrolysis provides the energy needed to return the transporter to the inward-facing position so that the transport can begin a new transport cycle[62].

ABCG2 structure and efflux function

The ABCG2 protein is a homodimer. Each monomer has six transmembrane helices and an NBD. The monomers dimerize, forming a transporter with a hydrophobic drug cavity that accommodates a diverse number of compounds with different structures and conformations[63]. The ABCG2 hydrophobic cavity is smaller and more substrate-selective compared to ABCB1[64]. Thus, the ABCG2 transporter selectively binds to a narrower range of substrates that are smaller, more hydrophobic, and planar. However, the NBD mediates ATP binding and hydrolysis to facilitate compound efflux by an inward-outward altering mechanism. Thus, the substrate in the intracellular space will first bind to the hydrophobic cavity, whereas the ABCG2 transporter is in the inward-facing conformation[64]. This process induces conformational changes in the NBD, resulting in productive ATP binding and hydrolysis. The energy produced induces conformational changes by an outward-facing conformation of ABCG2 and translocation of the substrate to the outside and subsequent release in the extracellular space. The transporter returns to its original inward conformation in the final step of substrate transport due to the binding and hydrolysis of ATP[64].

The different types of brain cancers will be discussed in the sections below, followed by discussing the role of ABCB1 and ABCG2 in brain function and the potential importance for mediating resistance to some anticancer drugs.

Brain tumors

Intracranial tumor term describes several irregular masses or neoplasms in which cells proliferate and reproduce rapidly and are unaffected by the processes that normally control cell growth[65]. There are > 150 different types of brain tumors that can be described as primary and metastatic tumors[65-68]. Tumors that arise from brain tissues or nearby areas are known as primary brain tumors[69], which frequently involve glial and non-glial cells. The latter class includes tumors that form from Schwann cells, the meninges, blood vessels, and endocrine glands, and are directly attached to cells in the central nervous system[68]. Primary tumors can be broadly classified as benign or malignant[68,69]. Benign tumors remain confined to original locations without invading other body sites[70]. In contrast, a malignant tumor can invade surrounding normal tissues and spread throughout the body *via* the circulatory or lymphatic systems[71]. Brain and other nervous system tumors are leading causes of cancer deaths among men < 40 years of age and women < 20 years of age, according to the American Cancer Society[72]. In addition, brain and other nervous system tumors are the second most common cancers in children after leukemia, accounting for 25% of all cancer cases[73]. Approximately 25,400 brain and other nervous system cancer cases occurred in 2024, leading to approximately 18,760 deaths[74]. It has been predicted that by 2040 brain cancer will rank among the top 4 types of cancer for cancer-related deaths (along with colorectal, breast, and lung

cancer) in male and female adults 20–49 years of age[75]. One of the most common and devastating primary brain tumors is glioblastoma multiforme (GBM). This type of tumor is highly resistant to chemotherapy and has a 5-year survival rate of only 32.5%[76]. Brain tumors are one of the most devastating and life-threatening cancers because of the important functions of the central nervous system (CNS)[65,77]. Unfortunately, patients with brain tumors are at high risk of neurological complications, including seizures, thromboembolic disease and peritumoral edema[78-80].

Benign tumors include chordomas[81,82], craniopharyngiomas[83-86], gangliocytomas[87,88], glomus tumors[89-91], meningiomas[92,93], pineocytomas[94,95], pituitary adenomas[72,96-98], and schwannomas[99,100].

Malignant brain tumors

Gliomas, which occur in the glia, are the most common type of malignant brain tumors in adults, accounting for 81% of all malignant brain tumors[101]. Brain tumors can also result from cancer cells in astrocytes, ependymal cells, and oligodendrocytes[102]. Examples of glial tumors include astrocytomas, ependymomas, GBM, medulloblastomas, and oligodendrogliomas.

Astrocytomas

Astrocytomas are the most prevalent gliomas, accounting for approximately 65% of all primary brain and spinal cord malignancies[103,104]. Astrocytomas arise from astrocytes, which are star-shaped glial cells that are a major component of the BBB[103]. Astrocytomas can form in any area of the brain but most commonly occur in the cerebrum. Astrocytomas can affect people of any age but are more common in adults, especially middle-aged males[103,104].

Ependymomas

Ependymomas are a type of brain tumor that develops when the ependymal cells that line the ventricular system undergo neoplastic transformation[105]. Ependymomas account for 2%–9% of all brain cancers and up to 12% of pediatric brain tumors[106]. The majority of ependymomas are well-defined, based on the anatomic location, which is typically the ventricular system[105].

GBM

GBM is the most invasive type of glial tumor[107]. These tumors develop rapidly, spread to other parts of the body, and have a poor prognosis[108]. GBMs are comprised of a variety of cells, including astrocytes and oligodendrocytes[107]. GBMs are more common in men than in women and primarily affect persons between 50 and 70 years of age[109]. Approximately 49.1% of all primary malignant brain tumors are GBMs[110].

Medulloblastomas

Medulloblastomas are tumors that develop in the cerebellum and are common malignant brain tumors[111]. Twenty percent of all childhood brain tumors are medulloblastomas[112]. Although medulloblastomas are high-grade tumors, medulloblastomas can be treated efficaciously using radiation and chemotherapy[113], although high rates of recurrence can occur after successful treatment[114].

Oligodendrogliomas

Oligodendrogliomas arise from the cells that produce myelin. Oligodendrogliomas account for approximately 5% of all primary intracranial tumors[115]. Other types of primary brain tumors include hemangioblastomas, which are slow-growing tumors most often occurring in the cerebellum[116], and rhabdoid tumors, which are extremely rare and severe tumors that develop throughout the central nervous system[117,118].

Metastatic brain tumors

Tumors that originate in the body (such as the breast or lungs) and spread to the brain through the circulation, are referred to as metastatic brain tumors[119]. Nearly one in every four cancer patients in the United States develops metastatic tumors in the brain[119]. Lung cancer patients may develop metastatic brain tumors in up to 40% of cases[120]. In the past, patients diagnosed with these malignancies typically had a poor prognosis with survival rates of a few weeks[121]. Currently, improved diagnostic technologies, combined with innovative surgical and radiation approaches, have increased survival rates to several years and improved the quality of life of the patients after diagnosis[122].

Brain tumors and ABC transporters

The BBB becomes a blood-tumor barrier (BTB) in brain tumors

The normal physiology of the BBB and associated ABC transporters is significantly changed by brain tumors. Cancer cells can displace endothelial cells of the BBB, disrupt the BBB integrity, and significantly alter the passage of solutes and compounds into the nervous system[45]. Alterations in the permeability of the BBB occur in primary and metastatic brain tumors[123], although the

extent of the disruption varies substantially. For example, there is only a minimal disruption of permeability in low-grade glioblastomas[124]. However, as tumors progress to a high-grade status, the BBB is significantly disrupted, endothelial tight junctions are separated, astrocytic processes are dissociated, and pericytes are recruited (**Figure 2**)[125]. These changes form the BTB[125,126]. Disruption of the BBB in glioblastomas occurs deep inside the center of the tumor where formation of new leaky blood vessels from microvascular proliferation occurs[127]. In contrast, the BBB is tight and more intact in peripheral portions of the tumor and the adjacent brain structures[128]. An intact BBB prevents endogenous and exogenous toxins from entering the brain[125,126]. However, the BTB prevents therapeutic drugs from accumulating within the brain in brain tumors, thereby limiting therapeutic efficacy[129].

The development of MDR is another factor that limits the efficacy of anticancer drugs[130,131]. MDR is the resistance of cancer cells to different types of anticancer drugs, although the anticancer drugs have substantially different chemical structures and mechanisms of acton[132]. MDR can be divided into different types based on the mechanism of action[43].

Role of ABC transporters in producing MDR in brain tumors

Although anticancer drugs are efficacious in treating many types of peripheral tumors, the success of these therapies is significantly limited for the treatment of brain tumors,

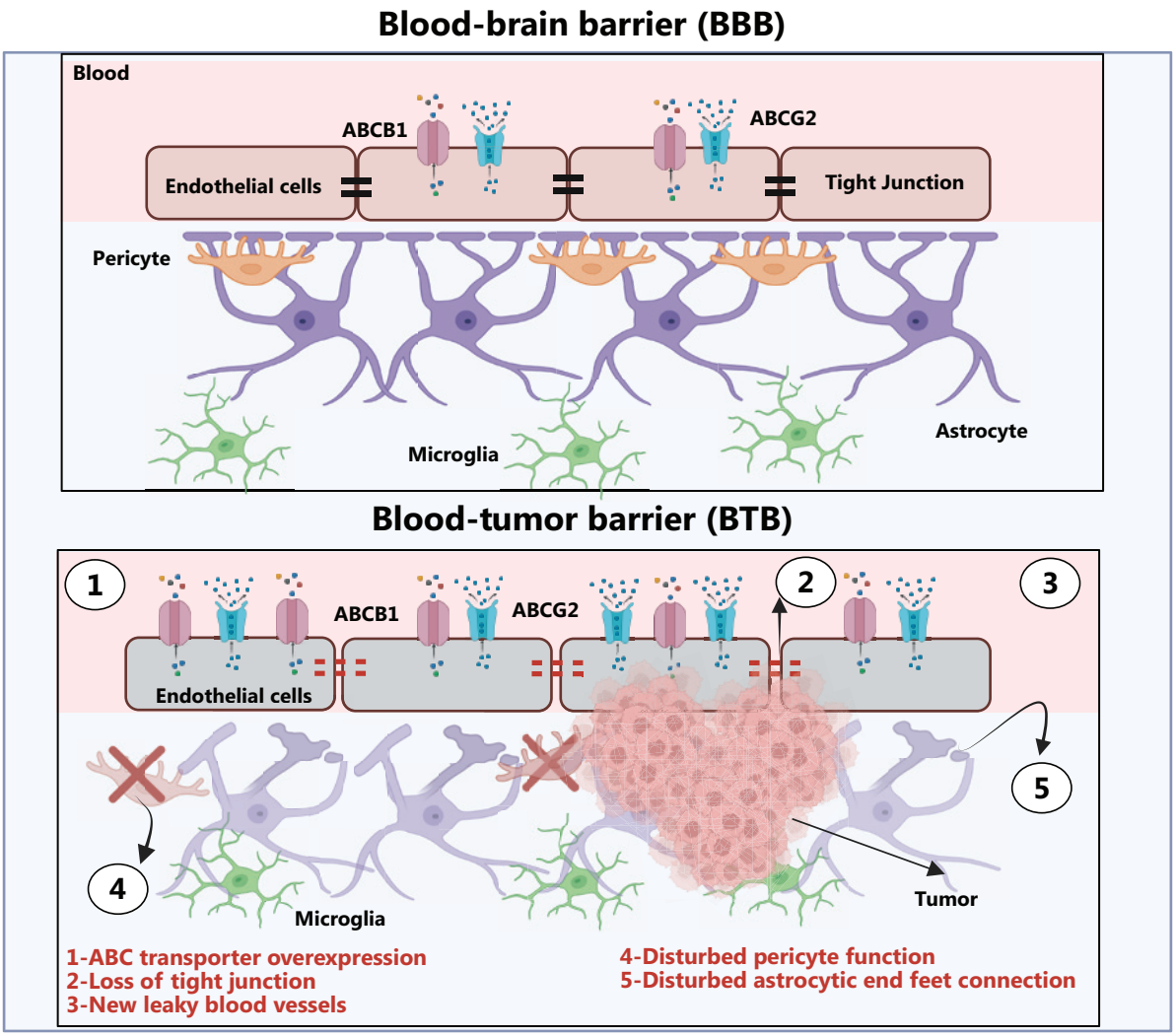


Figure 2 Blood-brain barrier (BBB) *vs.* blood-tumor barrier (BTB). The BTB has a loss of endothelial tight junctions, microvascular proliferation forming new leaky blood vessels, altered astrocytic end feet connections, and altered pericyte function. Importantly, the ABCB1 and ABCG2 transporters are overexpressed in the membranes of brain tumor cells, producing a second barrier to the efficacious treatment of brain tumors.

primarily due to poor delivery of the drug to the tumor[126]. Consequently, many otherwise highly efficacious anticancer drugs do not reach concentrations required to efficaciously treat metastatic brain tumors[45].

MDR to anticancer drugs can be intrinsic (primary) or extrinsic (secondary)[133]. Intrinsic MDR occurs when there has been no previous exposure to the anticancer drug or drugs and is caused by genetic or epigenetic factors. Extrinsic MDR can result from the overexpression of specific efflux transporters, a reduction of apoptosis, enhanced DNA damage repair mechanisms, induction of autophagy, cancer stem cell dysregulation, miRNA and other epigenetic abnormalities, and the induction of hypoxia[134].

Cancer stem cells or cancer progenitor cells are terms used to describe drug resistant sub-populations of cancer cells that facilitate tumor progression and recurrence[135]. These stem cells can produce significant treatment failure and high relapse rates in brain cancer[136]. Studies have reported that ABC transporters have a vital role in drug resistance mechanisms with MDR resistance stem cells derived from various brain tumor tissues, thus producing the development of intrinsic and extrinsic MDR in these tissues[136].

The BBB varies from intact to absent in brain tumors but de Gooijer et al.[49] reported that even when the tumor has leaky blood vessels, the expression of transporters can still decrease the efficacy of chemotherapy[49]. The increase in the expression of ABC transporters, including ABCB1 and ABCG2, in glioma cells has been reported to produce MDR. The removal of brain tumors from four patients indicated that ABCB1 and ABCG2 transporters were significantly overexpressed in isolated brain tumor tissues[137]. Transporter overexpression limits anticancer drug accumulation, thereby producing drug resistance. For example, these mechanisms can produce resistance to doxorubicin, etoposide, and methotrexate[19]. Therefore, ABC transporter expression is now considered to be a potential prognostic biomarker for brain tumor response to treatment. Indeed, ABCC1, ABCC3, and ABCG2 transporter overexpression is a biomarker for poor response to chemotherapy treatment of GBM[138].

In the sections below, the roles of ABCB1 and ABCG2 in decreasing or abrogating the efficacy of anticancer drugs used to treat brain tumors are discussed.

ABCB1

It has been reported that ABCB1 expression is significantly increased in endothelial cells in brain tumors[115]. A study of primary medulloblastoma brain tumors in patients from the United Kingdom, Russia, and Germany indicated that 43% of the tumor samples had a high level of ABCB1 expression[115]. Furthermore, there was a significant correlation between the level of ABCB1 expression and high risk of tumors with poor prognosis[111]. It is important to note that the four anticancer drugs currently approved for medulloblastomas are substrates of the ABCB1 transporter[139]. CD133 is a neural stem cell marker that is a known prognostic marker for brain tumors[140]. CD133 expression in gliomas varies among studies. CD133 expression increased from single cells in lower-grade brain tumors to patches of cells in grade IV brain tumors, and its presence is predictive of progression and relapse in grade II and III brain tumors[141]. In a previous study, ABCB1 transporter expression was determined in samples of ependymoma primary brain tumors and co-stained with CD133[136]. At least 0.28% of the cells stained positive for the ABCB1 transporter and the ABCB1-stained tumors frequently contained CD133 (0.21% of cells), suggesting that drug-resistant cells are a subset of the cancer stem cell subpopulation[136].

Based on the role of ABCB1 in ependymomas, medulloblastoma and gliomas, it could be hypothesized that the use of drugs that inhibit ABCB1 in combination with anticancer drugs that are ABCB1 substrates, could aid in treating high-risk, resistant, and relapsed brain tumors. A limited number of clinical studies have been conducted involving these medical conditions. A clinical study in 2006 reported the effect of tamoxifen (a non-toxic ABCB1 inhibitor) on the efficacy of paclitaxel in 27 patients undergoing surgical resection of primary or metastatic brain tumors[142]. The patients received paclitaxel (175 mg/m^2 iv) or tamoxifen for 5 d followed by paclitaxel. The results showed no significant differences in the concentration of paclitaxel between the two treatment groups[142]. Another phase I clinical study reported the effect of the ABCB1 inhibitor, tariquidar, in combination with vinorelbine. Twenty-six patients with different types of carcinomas were included in the study. Vinorelbine (20 mg/m^2, i.v.) was administered on days 1 and 8 at a single dose of tariquidar (150 mg over 30 min prior to vinorelbine). Tariquidar significantly decreased the hepatic clearance of 99mTc-sestamibi (a radioactive tracer used in nuclear medicine imaging), a finding consistent with the inhibition of hepatic ABCB1[143]. Tariquidar significantly decreased ABCB1-mediated rhodamine efflux from CD56+ cells. However, none of the patients had primary or metastatic brain tumors[143]. It has been reported that verapamil and vardenafil are efficacious inhibitors of the ABCB1 transporter[136]. The efficacy of the anti-cancer drug, etoposide,

was shown to be significantly increased in ABCB1-expressing medulloblastoma cell lines when etoposide was combined with verapamil and vardenafil[111]. The delivery of adriamycin and herceptin to the brain in rodents with primary brain tumors was increased when co-administered with vardenafil[144] and this effect also occurred in metastatic brain tumor models[145].

Temozolomide is an anticancer drug that is used extensively in combination with radiotherapy as a first-line treatment regimen for high-grade glioblastomas[146]. Temozolomide was designed to permeate the BBB, which facilitated anticancer efficacy in glioblastomas[147]. However, some studies reported an increase in the bioavailability of temozolomide in the brain when combined with some inhibitors of ABC transporters[147,148]. An *in vitro* study indicated that temozolomide is a poor substrate for ABCB1 in porcine kidney LLC-PK1 cells expressing the murine ABCB1 transduced subclone, LLC-Mdr1a[147]. However, the BBB penetration of temozolomide *in vivo* was 20% greater in *Abcb1a/b* knockout mice compared to wild type (WT) mice[147]. These results suggested that using an ABCB1 inhibitor with temozolomide could increase the efficacy of temozolomide in the treatment of high-grade glioblastomas. This finding was further validated when temozolomide was combined with the dual ABCB1/ABCG2 inhibitor, elacridar. Elacridar significantly increases temozolomide penetration across the BBB in WT mice[147]. A recent study characterized different models of intracranial tumors and used four *in vivo* models that represented a spectrum of vasculature leakiness from minimal-to-highly leaky tumors: GBM8 (minimum or no leakiness), Mel57 (not fully intact with limited leakiness), Mel57VEGF (significant leakiness); and U87 (highly vascularized and significant leakiness). The penetration of docetaxel could be limited in these tumors by an increased expression of the ABCB1 transporter despite the leakiness. Thus, BBB leakiness did not significantly correlate with the unimpeded access of ABC substrate drugs to brain tumors[49].

Experiments were performed in an orthotopic brain tumor mouse model (formed by the intracerebral inoculation of U-87 MG-Luc2 glioma cells) to determine if BBB penetration and efficacy of the ABCB1 inhibitor, HM30181A (10 mg/kg iv), was increased by HM30181A formulation in hydroxypropyl-β-cyclodextrin (cyclodextrin-HM) when co-administered with paclitaxel (10 mg/kg, i.v.). The treatment started on day 6 post-inoculation by tail vein injection (q4d × 5). This combination significantly increased the efficacy of paclitaxel based on a significant decrease in bioluminescence signals (indicating a decrease in the size of the tumors) in a dose-dependent manner compared to mice treated with paclitaxel alone or vehicle ($P < 0.05$). Moreover, the life span of co-treated mice groups was significantly longer than other groups. Specifically, the median survival time of the co-treated mice was 39 d (an increase in lifespan by 18%; $P = 0.014$), while the median survival time was 35 d for paclitaxel alone (an increase in lifespan by 6%; $P = 0.900$)[149]. It was reported that an increased expression of the ABCC transporter in tumor samples occurred in 16 of 23 untreated patients and the proportion of ABCC-positive cells in the total cell population was 3%–32% in the 16 ABCC-positive patients[150]. ABCB1-positive tumors were present in 4 of the 23 patients and the proportion of ABCB1-positive cells in the total cell population was 4%–23%, suggesting that the ABCB1 transporter mediated chemotherapy resistance in glioma patients[151]. Data suggested that the ABCB1 transporter in brain tumors may also have a role in metastasis. Studies in metastatic tumors indicated that the presence of ABC transporters at the BBB and/or BTB of primary tumors is a major contributor to drug resistance and residual ABC transporter function at the BTB is sufficient to limit drug cytotoxicity[17]. Several studies have reported a significant negative correlation between the level of ABCB1 transporter expression and brain tumor metastasis[136,150,152]. This finding could be due, in part, to the ABCB1 transporter efflux of paracrine factors released by the tumor microenvironment that are involved in inhibiting metastasis[136,150,152].

ABCG2

ABCG2 limits the entry of various anticancer drugs into the brains of patients undergoing treatment[153]. There are a limited number of clinical studies published involving the effect of ABCG2 transporter inhibition in brain tumors. A study involving six patients with advanced solid tumors was conducted to assess the efficacy of elacridar, an inhibitor of the ABCB1 and ABCG2 transporters[154], on the distribution of ^{11}C-erlotinib [a radiolabeled version of erlotinib used in positron emission tomography (PET) imaging] in the brain, as an indicator of CNS penetration[155]. The patients underwent ^{11}C-erlotinib PET scans before and after a 1,000 mg oral dose of elacridar. The volume of distribution of ^{11}C-erlotinib was quantified to assess brain uptake. The volume of distribution of ^{11}C-erlotinib did not significantly increase after the administration of elacridar (0.213 ± 0.12 *vs*. 0.205 ± 0.07; $P = 0.91$)[155]. Another clinical study

investigated the efficacy of supratherapeutic-doses of oral erlotinib to inhibit the ABCB1 and ABCG2 transporters at the human BBB[142]. Healthy male volunteers underwent two consecutive PET scans with ^{11}C-erlotinib: a baseline scan; and a second scan with a concurrent i.v. infusion of the ABCB1 inhibitor, tariquidar (3.75 mg/min, n = 5), or after the oral administration of single ascending doses of erlotinib (300 mg, n = 7; 650 mg, n = 8; or 1,000 mg, n = 2). The administration of tariquidar did not significantly alter the brain distribution of ^{11}C-erlotinib brain distribution compared to patients who did not receive tariquidar (baseline scan). Thus, ABCB1 inhibition alone was not efficacious in increasing the brain levels of ^{11}C-erlotinib. However, oral erlotinib, at 650mg, produced a partial saturation of ABCG2 and ABCB1 transporter activity, as indicated by a significant increase in the levels of ^{11}C-erlotinib, based on the following: increased volume of distribution (23% ± 13%, P = 0.008), influx rate constant of radioactivity from plasma into brain (58% ± 26%, P = 0.008) and area under the brain time–activity curve (78% ± 17%, P = 0.008)[142].

In contrast to studies in humans, numerous preclinical *in vitro and in vivo* studies have reported that ABCG2 transporter inhibition produced significant increases in the level of some anticancer drugs in the brain that is correlated with an increase in anticancer efficacy[156].

A major discrepancy between the preclinical and clinical data regarding the inhibition of ABC transporters could be attributed to the complexity of the tumor microenvironment in humans. Preclinical studies cannot fully replicate this complexity, such as hypoxia and immune cell interactions. Genetic and phenotypic variability can also alter the expression of ABC transporters in clinical studies. Consequently, the results can be significantly different from the results obtained in preclinical models of brain tumors[157]. Furthermore, there could be significant differences in the pharmacokinetic profile of compounds between humans and the animal species in the preclinical models[158]. Finally, in humans, there are numerous proteins in addition to ABC transporters that can give rise to MDR. Thus, efflux-independent drug resistance mechanisms could compensate for the inhibition of the ABC transporters, thereby facilitating the survival of cancer cells[159].

Photodynamic therapy (PDT) is a novel treatment approach that utilizes a tumor-selective photosensitizer precursor, 5-aminolevulinic acid [(5-ALA), gliolan®]. This results in the formation of the fluorescent and phototoxic compound, protoporphyrin IX (PpIX), which increases the levels of reactive oxygen species (ROS) in gliomas, oral cancer, and breast cancer[160]. However, PpIX is a substrate of the ABCG2 transporter[156]. Therefore, ABCG2 transporter overexpression in glioblastoma cells limits the efficacy of PDT, whereas a decrease in ABCG2 transporter expression in glioblastoma cells restores the efficacy of PDT in these cells[153]. Another photosensitizer, chlorin e6, is also a substrate of the ABCG2 transporter[161]. The overexpression of the ABCG2 transporter in the glioblastoma cell line, U87, or doxycycline-induced ABCG2 overexpression in U251 cells, produced a 6-fold decrease in the levels of chlorin e6[161]. The ABCG2 inhibitor, KO143, restored the efficacy of chlorin e6 in the cell lines by increasing the accumulation of chlorin e6[161].

An *in vitro* study reported that temozolomide (a drug used to treat glioblastomas) is a substrate for the ABCG2 transporter in parental canine MDCKII cells and the Bcrp1-transduced (MDCKII-Bcrp1) subline[147]. The results of this study indicated that the *in vivo* BBB penetration of temozolomide was significantly greater in knockout mouse models compared to the *WT* mice. The BBB temozolomide levels were increased by 20% and 50% in *Abcg2*$^{-/-}$ and *Abcb1a/b*$^{-/-}$, respectively, compared to WT mice. The combination effect of the genetic mutations clearly indicates the overlap between substrate affinities and the redundancies in the activity of the transporters that must be overcome to eliminate drug resistance.

Gefitinib is an epidermal growth factor receptor (EGFR) inhibitor that was extensively investigated for the treatment of high-grade gliomas[162]. The accumulation of gefitinib in the brains of WT Friend leukemia virus strain B (FVB/N) mice was very low but was increased by the deletion of ABC transporters based on data in *Mdr1a/b*$^{(-/-)}$ *Bcrp1*$^{(-/-)}$ *mice*[162]. The brain-to-plasma (B/P) concentration ratios were 70-fold higher in the *Mdr1a/b*$^{(-/-)}$ *Bcrp1*$^{(-/-)}$ mice compared to WT mice, although leakiness of the BBB was not signficantly-altered between the groups. Elacridar, a dual inhibitor of the ABCB1 and ABCG2 transporters[154], has been reported to increase gefitinib accumulation in the brain. This finding was confirmed by the results which showed that in WT mice treated with elacridar, the B/P concentration ratios of gefitinib was increased by more than 4-fold compared to mice not treated with elacridar[162]. **Table 3** summarizes the preclinical studies that determined

the effect of ABC transporter inhibitors on the levels of drugs in the brain.

History of the development of ABC transporter inhibitors for use in reversal of MDR and associated challenges

Over the last 5 decades, ABCB1 and ABCG2 inhibitors were developed to increase the efficacy of some anticancer drugs, by increasing the accumulation in different organs and tissues, thereby significantly decreasing or reversing MDR[185]. This advance ultimately led to the preclinical and clinical development of different generations of ABC transporter inhibitors. The first-generation inhibitors included the drugs, verapamil and cyclosporine, which inhibit ABCB1 and ABCG2, respectively, and were originally developed to treat some non-cancerous diseases[186]. Subsequently, studies confirmed that these compounds inhibited ABC transporters. However, the plasma levels of these compounds were insufficient to efficaciously inhibit the above mentioned transporters and severe adverse effects were produced[186]. For example, verapamil did not have non-ABCB1 selectivity and had very low potency in inhibiting the ABCB1 transporter and high concentrations were required to produce an efficacious inhibition. The concentration needed was significantly higher than previously approved therapeutic concentrations and was associated with significant toxicities. Furthermore, verapamil had multiple drug-drug interactions with certain anticancer drugs. Second generation ABCB1 and ABCG2 inhibitors were developed with improved selectivity, such as PSC 833, GG918, and S9788. The compounds were developed and evaluated but had unsuitable or problematic pharmacokinetic profiles and limited efficacy in increasing the anticancer efficacy of certain drugs[187].

PSC 833, also known as valspodar, was evaluated in several clinical studies[188,189]. PSC 833 significantly inhibited the CYP3A4 enzyme, subsequently altering the metabolism of some chemotherapeutic drugs and inducing additional toxicities. For example, the addition of valspodar to a 4 day infusion of vincristine, doxorubicin, and an oral dose of dexamethasone did not significantly improve the clinical outcomes in multiple myeloma patients[188]. Furthermore, the incidence and severity of adverse and toxic effects were increased in the combination treatment group. Toxicities included neurotoxicity, adverse GI effects, and an increase in the liver enzyme levels. Another clinical study reported that the addition of valspodar to paclitaxel for the treatment of advanced ovarian cancer only produced a limited clinical benefit[189]. As a result of the poor efficacy and toxicity produced by the second-generation inhibitors, a third generation of ABCB1 and ABCG2 inhibitors was developed. One of these drugs, tariquidar[187], is a selective ABCB1 inhibitor that has acceptable solubility with an acceptable therapeutic index[187]. However, tariquidar had poor efficacy in inhibiting ABCG2 transporters[166] and clinical studies indicated that tariquidar had a limited role in increasing the efficacy of anthracycline or taxane in cancer cells, such as breast cancer and non-small cell lung cancer (NSCLC)[187].

Erlotinib, which inhibits EGFR, is also a potent inhibitor of the ABCG2 transporter[190]. Erlotinib has been reported to increase the *in vitro* accumulation of [^{3}H]-mitoxantrone in cancer cells expressing WT or mutated forms of the ABCG2 protein {WT ABCG2 [arginine at 482 position]-overexpressing drug-resistant breast cancer cell line, MCF-7/FLV1000, and mutated ABCG2 [arginine →threonine (T) at amino acid 482 position}-overexpressing drug-resistant breast cancer cell line, MCF-7/AdVp3000[191]. In contrast, erlotinib did not significantly increase the intracellular accumulation of [^{3}H]-mitoxantrone in the flavopiridol-resistant cell line, S1/FLV5000, which does not express the ABCG2 transporter[191]. Elacridar is highly efficacious in inhibiting the ABCB1 and ABCG2[154]. However, elacridar has poor oral bioavailability and does not reach *in vivo* concentrations required to significantly inhibit ABCB1 and ABCG2 transporters in the BBB[55]. Use of elacridar is also limited by poor solubility that requires elacridar to be used with tetrahydrofuran, which is toxic and unacceptable for use in humans[55].

A study reported that the CNS distribution of [^{11C}] erlotinib was significantly increased by known ABCB1 and/or ABCB2 inhibitors. The distribution volume in brain ($V_{T,brain}$) of [^{11C}] erlotinib was increased by the administration of 21.5 mg/kg of tariquidar (69%) and 43 mg/kg of erlotinib (19%), respectively. Furthermore, the $V_{T,brain}$ of [^{11C}]erlotinib was increased by imatinib (22%), lapatinib (25%), and cyclosporine A (49%)[166]. However, the increase in the brain levels of [^{11C}]erlotinib from the aforementioned drugs was significantly less than that produced in a dual knockdown murine model [Abcb1a/b$^{(-/-)}$/

Table 3 A summary of preclinical studies investigating the effect of ABC transporter inhibitors on the brain and the blood-brain barrier

Cyclosporin A (ABCB1, ABCC1, ABCC2, and ABCG2)[163]	
• Cyclosporin A increased the brain uptake of paclitaxel and docetaxel in wild-type mice up to 3-fold and significantly increased their plasma levels.	164,165
• [^{11}C] erlotinib total distribution volume in the brain was increased in mice treated with cyclosporin A (+49%). Cyclosporin A also increased blood concentrations measured at the end of the PET scan (101%).	166
• Cyclosporin A decreased the clearance of doxorubicin by 42% in monkeys and increased doxorubicin plasma concentrations. However, doxorubicin levels in the CSF were not increased.	167
Valspodar (ABCB1 and ABCC2)[168]	
• Valspodar increased the accumulation of docetaxel and paclitaxel in the mouse brain by 3.5- and 5-fold, respectively, and increased the plasma levels by 73% and 83%, respectively.	165,168
• Valspodar increased the brain accumulation of radioactive verapamil in monkeys by 4.6-fold but did not affect blood levels.	169
Zosuquidar (ABCB1)[170]	
• Zosuquidar increased the accumulation of paclitaxel in the brain by 5-fold in mice, which was associated with a 56% increase in the plasma levels of paclitaxel.	171
Tariquidar (ABCB1 and ABCG2)[172]	
• In mice, tariquidar increased the brain-to-plasma ratio of tacrolimus by 14-fold after focal cerebral ischemia but only 12-fold in non-ischemic brains. There was no significant change in the blood levels of tacrolimus.	173
• Tariquidar increased the total distribution volume of [^{11}C]erlotinib in the brain compared to vehicle-treated mice (69%). This was correlated with higher plasma levels of [^{11}C]erlotinib, compared to clinically achievable plasma concentrations.	166
• Tariquidar increased the concentration of [^{18}F] paclitaxel in the liver (54%) and lungs (97%) in rhesus monkeys normalized to plasma levels but had no effect on the brain levels of tariquidar.	174
Elacridar (ABCB1 and ABCG2)[175,176]	
• Elacridar increased the brain uptake of paclitaxel by 5-fold in mice but did not significantly alter its plasma concentration.	164
• Elacridar significantly increased the brain concentrations of docetaxel in wild-type mice by 3.6-fold but did not significantly alter its plasma concentration.	165
• Elacridar significantly increased pazopanib brain penetration in FVB mice by 5-fold compared to vehicle control without significantly altering the plasma concentrations of pazopanib.	177
• Elacridar treatment increased sunitinib brain accumulation in wild-type mice (12-fold) to levels equal to the levels in *Abcb1a/1b/Abcg2*−bcb1a/1b mice.	178
• Elacridar increased the plasma levels and brain accumulation of selitrectinib in wild-type mice by 1.6-fold, similar to that occurring in *Abcb1a/1b; Abcg2***−/−** mice.	179
• The co-administration of elacridar produced an 11-fold increase in the brain levels of veliparib (ABT-888) in wild-type mice. The brain/plasma concentration ratio was similar to that of *Abcb1a/1b*−bc*; Abcg2*− Abcg21b mice, compared to mice, after the wild-type controls.	148
• In contrast to the non-significant effect on plasma concentrations, elacridar increased the brain concentration of dasatinib in wild-type mice by 10-fold. Th co-administration of dasatinib with elacridar to wild-type mice produced dasatinib brain levels like the levels in Abcb1a/1b; Abcg2**−/−** mice.	180
Tyrosine kinase inhibitors (ABCB1, ABCG2, and BCRP1)[181-184]	
• Erlotinib and canertinib inhibited the directionality of pazopanib efflux *in vitro* and increased the brain levels of pazopanib (2.0–2.5-fold) in FVB mice, without significantly altering plasma concentrations.	177
• The tyrosine kinase inhibitors produced a lower increase in the total distribution volume of [^{11}C] erlotinib in the brains of mice treated with erlotinib (23%), imatinib (22%), and lapatinib (25%) compared to Abcb1a/b**(−/−)** Abcg2**(−/−)** mice (149%).	166

Abcg2$^{(-/-)}$] (149%). Thus, none of the evaluated drugs achieved sufficient levels of inhibition that are likely to produce significant therapeutic efficacy.

Despite the significant efforts to develop potent and safe ABCB1 and/or ABCG2 inhibitors, none of these drugs produced beneficial clinical results needed to overcome MDR in tumors expressing these ABC transporters (**Figure 3**).

Clinical studies involving these compounds reported limited or poor efficacy and the therapeutic outcomes in patients failed to significantly improve after the addition of these compounds to their regimens. Furthermore, some of these compounds produced severe adverse effects and/or toxicities. These compounds also had unsuitable pharmacokinetic profiles, including poor oral bioavailability and the plasma concentrations were too low to produce therapeutic efficacy and most importantly had limited BBB penetration[192]. **Table 4** shows some important clinical trials that were conducted to evaluate the efficacy of drugs in inhibiting ABC transporters.

Advances in the development of ABCB1 and ABCG2 inhibitors

To overcome MDR in cancer patients, innovative strategies are emerging in response to the above-mentioned issues. These include light-based therapies, such as PDT, nanomedicine, RNA interference (RNAi), and gene editing using clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9). Using light irradiation and photosensitizers, PDT produces ROS that can effectively kill cancer cells[197]. A recent study reported that photosensitizers, such as redaporfin, a benzoporphyrin derivative that interacts with the ABCB1 and ABCG2 transporters, may represent promising new approaches[198,199]. The compound, rose Bengal [4-(3,5-dibromo-2,4,6-triiodophenyl)-2,5-cyclohexadien-1-one], targets the ABCB1, ABCG2, and MRP1 transporters[200].

Nanomedicine is another promising approach that utilizes nanoparticles to increase drug delivery, increase stability, and produce sustained drug release, which are key factors in overcoming drug efflux[201]. Examples of nanomedicines include mesoporous silica nanoparticles (MSN), poly-lactic acid (PLA) nanoparticles, and graphene quantum dots (GQDs)[202,203]. These nanoparticles have been successfully combined with anticancer drugs, such as doxorubicin, to inhibit the ABCB1 transporter[202,203]. Clinically approved nano-formulations, such as Doxil, Lipusu, and Abraxane, are indicative of the potential of nanomedicines to overcome MDR in tumors[197,204]. Nanoparticles can be used to increase the levels of drug in tumors, while minimizing systemic adverse effects[205]. Nanocarriers can be designed to bypass or modulate ABC transporters, thereby increasing drug levels in cancer cells.

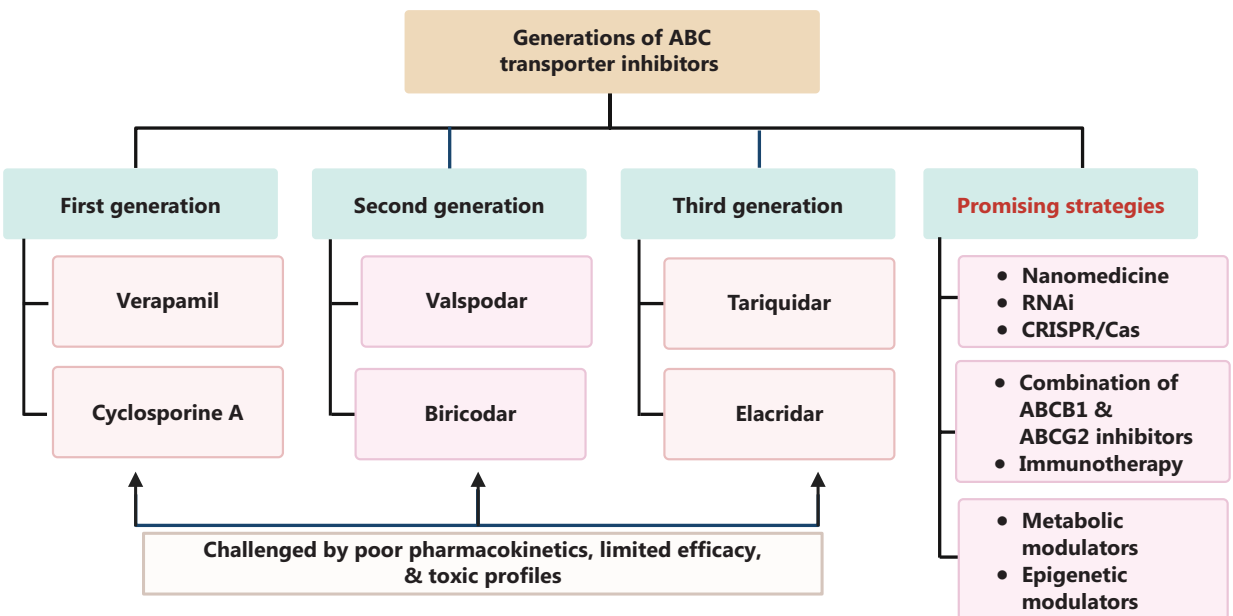


Figure 3 The history of the development of ABC transporter inhibitors, associated challenges, and promising strategies for targeting ABC transporters to reverse MDR in cancer.

Table 4 Important human studies investigating ABCB1 and or ABCG2 inhibitors

Clinical studies on ABCB1 and or ABCG2 inhibitors	Phase	Results
Cyclosporin A: Imaging technique to measure P-gp activity using ^{11}C-verapamil as the P-gp substrate and cyclosporin as the P-gp inhibitor in healthy volunteers[193].	–	Cyclosporin A produced an 88% increase in the brain-to-blood ratio (AUC) of ^{11}C-radioactive verapamil.
Erlotinib: A supratherapeutic-dose of oral erlotinib inhibited ABCB1/ABCG2 activity at the human BBB[194].	–	A 650 mg oral dose produced a significant increase in the volume of distribution, the influx rate constant of radioactivity from plasma into the brain and area under the brain time-activity curve of ^{11}C-erlotinib. Treatment efficacy was not determined.
Elacridar: To investigate the effects of the ABCB1 and ABCG2 inhibitor, elacridar, on the brain uptake using ^{11}C-erlotinib PET[155].	–	The brain uptake of ^{11}C-erlotinib was not increased after the administration of elacridar. Treatment efficacy was not determined.
Elacridar: Study of Elacridar (GF120918) and oral Topotecan in cancer patients[195]	I	The administration of 100 mg of elacridar with oral topotecan produced complete oral bioavailability of topotecan. The recommended oral dose of topotecan is 2.0 mg daily, times 5, every 21 days. Treatment efficacy was not determined.
Elacridar: Co-administration with paclitaxel to assess the systemic exposure to oral paclitaxel in cancer patients[196].	–	The oral combination of paclitaxel with elacridar was well-tolerated. The increase in the systemic exposure to paclitaxel in the combination was similar in magnitude to the combination of elacridar and cyclosporin A. Treatment efficacy was not determined.
Valspodar: In combination with vincristine, doxorubicin, and dexamethasone (valspodar/VAD) *vs.* VAD alone in patients with recurring or refractory multiple myeloma (E1A95)[188].	III	The addition of valspodar to a 4 day infusion of vincristine, doxorubicin, and an oral dose of dexamethasone in multiple myeloma patients did not significantly improve the clinical outcomes.
Valspodar: Study of paclitaxel and valspodar (PSC 833) in refractory ovarian carcinoma in a gynecologic oncology group study[189].	II	The addition of valspodar to paclitaxel for the treatment of advanced ovarian cancer only produced a limited clinical benefit.
Tariquidar: A clinical study on the effect of the ABCB1 inhibitor, tariquidar, in combination with vinorelbine in 26 patients with different types of carcinomas were included in the study[143].	I	Vinorelbine (20 mg/m^2) was administered intravenously, on days 1 and 8 with a single dose of 150 mg of tariquidar (tariquidar was given over 30 min prior to vinorelbine). Tariquidar significantly decreased the hepatic clearance of 99mTc-sestamibi, a finding consistent with the inhibition of the hepatic ABCB1 transporter.
Tariquidar: The addition of the selective P-glycoprotein (P-gp) inhibitor tariquidar (XR9576) to chemotherapy could induce an objective tumor response in patients who previously were resistant to the same drugs[187].	II	Tariquidar only produced limited clinical efficacy in increasing the efficacy of anthracycline or taxane chemotherapy.

Studies have suggested that the preclinical data are encouraging the translation to the clinical stage[206,207] but the clinical application has been hindered by nanoparticle biodistribution and immunogenicity problems, which need to be explored further. Additional details regarding the challenges in the clinical translation of nanomedicines have been published[208,209].

RNAi, including small interfering RNA (siRNA), short hairpin RNA (shRNA), and microRNA (miRNA), represents another promising method for reversing MDR[210]. By silencing or regulating the expression of ABC transporter genes, RNAi can restore drug efficacy in resistant cancer cells. For example, miRNAs, such as miR-137, miR-145, and miR-200c, have been reported to inhibit the ABCB1 transporter, thereby resensitizing breast and colon cancer cells to doxorubicin and paclitaxel[211].

CRISPR/Cas9 gene editing has emerged as a leading technology in targeting MDR-related genes. The knockdown of the *abcb1* gene, using CRISPR/Cas9 significantly increased the

efficacy of the anticancer drugs, doxorubicin and temozolomide, in different types of cancer cells or tumors[212]. In breast cancer and glioblastoma models, this approach significantly increased the efficacy of doxorubicin and temozolomide, respectively[213]. These findings suggest that CRISPR/Cas9 has the potential to transform treatment outcomes for MDR cancers[211]. Despite these advances, concerns about CRISPR off-target effects and genomic instability, remain significant barriers to clinical translation[214,215]. Nevertheless, proof of the effective clinical application of CRISPR-engineered T cells in relapsed tumors[216] provides the groundwork for exploring similar strategies in MDR tumors.

Metabolic reprogramming is a unique feature in cancerous cells, which facilitates cell survival, abnormal proliferation, invasiveness, and metastasis. Several survival metabolic pathways are increased and altered in cancer, including, glycolysis, mitochondrial oxidative phosphorylation, glutamine metabolism, lipid metabolism, amino acid metabolism, autophagy, and micropinocytosis. Being recognized as a fundamental characteristic of cancer, metabolic reprogramming is currently being targeted by novel therapeutic approaches. Metabolic inhibitors, particularly those targeting glycolysis, are being investigated, including 2-deoxy-d-glucose (2-DG), 3-bromopyruvate (3-BrPA) and lonidamine {LN; 1-[(2,4-dichlorophenyl) methyl]-1H-indazole-3-carboxylic acid}. These compounds inhibit glycolysis, resulting in ATP depletion and induction of apoptosis[217]. Interestingly, by inhibiting glycolysis and decreasing ATP levels, ABC transporter function was inhibited by these compounds and increased the efficacy of daunorubicin and mitoxantrone in RPMI8226 (ABCG2 overexpressed), KG-1 (ABCB1 overexpressed), and HepG2 cells (ABCB1 and ABCG2 overexpressed)[218]. This finding may indicate that metabolic reprogramming inhibition could be used as a strategy for ABC transporter inhibition.

Epigenetic modifications, including DNA methylation and post-translational modification of histone, have been hypothesized to produce the overexpression of ABC transporters in cancer cells[219]. For example, global genomic hypomethylation was detected in CpG dinucleotides (CpGs) in repetitive elements in cancer. However, hypermethylation of the promoter region of tumor suppressor genes can be frequently present in cancer cells[220]. Similarly, epigenetic modifications were prevalent during the acquisition of drug resistance in cancer cells. Furthermore, in drug-resistant MCF-7-KCR and OV1/VCR multidrug-resistant ovarian carcinoma cells, there were global acetylation levels of histones and ABC transporter expression was significantly correlated with changes in DNA methylation patterns[219]. Thus, targeting epigenetic modifications can be an effective strategy to alter ABC transporter expression in cancer. The hypomethylation of the ABCB1 promoter was significantly correlated with overexpression of the ABCB1 transporter[220]. Consequently, epigenetic modulators, particularly epigenetic modulators that increase the activity of DNA methyltransferases, such as afatinib or melatonin, would result in hypermethylation and subsequent downregulation in ABC transporters expression, such as ABCB1 or ABCG2[220]. Importantly, a recent study suggested a new approach for inhibiting the ABCB1 and ABCG2 transporters[55]. The results of this study indicated that complete inhibition of the ABCB1 and ABCG2 transporters is required to increase the efficacy of anticancer drugs, which are often dual substrates of the ABCB1 and ABCG2 transporters, for the treatment of brain tumors, by increasing the CNS penetration of ABCB1 and ABCG2 substrate drugs. The co-administration of erlotinib, an ABCG2 inhibitor, and tariquidar, an ABCB1 inhibitor, produced an ABCB1/ABCG2 inhibition. The results indicated that this drug combination produced a 3-fold increase in the volume of distribution of [^{11C}]erlotinib in mice and a 3.4–5-fold increase in the volume of distribution in the brains of macaque monkeys. The combination treatment produced a significantly greater increase in the [^{11C}]erlotinib volume of distribution compared to erlotinib or tariquidar alone. **Table 4** summarizes the preclinical studies that determined the effect of ABC transporter inhibitors on the levels of drugs in the brain.

Another approach that could be successful in overcoming resistance and increasing the efficacy of treatment in cancer overexpressing ABC transporters involves combining ABC transporters inhibitors with immunotherapy. ABCB1 and ABCG2 transporters are crucial mediators of immunity and are often overexpressed in cancer-related tumor microenvironments[221]. These ABC transporters have a major role in mediating MDR in cancer cells and the modulation of immune responses through the efflux of immunomodulatory molecules, cytokines, and anticancer drugs[222]. Furthermore, the contribution to immune evasion has been correlated with the alteration of antigen presentation and resistance mechanisms that limit immune cell recognition and cytotoxicity[223]. Therefore, targeting ABC transporters in combination with immunotherapy could represent a novel treatment regimen to increase immune surveillance and overcoming drug resistance in cancer patients[221]. Lazertinib, a third-generation tyrosine

kinase inhibitor[224], inhibits the efflux activity of the ABCB1 and ABCG2 transporters, which increased the intracellular levels of doxorubicin in the treatment of liver cancer in *in vitro, ex vivo, and in vivo* HepG2 xenograft mouse models[223]. Although there are no studies with brain tumors, targeting ABC transporters with immunotherapy or targeting ABC transporters by small molecules, in combination with chemotherapy, holds promise for increasing immune surveillance and overcoming drug resistance in cancer patients. Clinical data indicates that the combined administration of immunotherapy and chemotherapy increased the therapeutic efficacy and decreased severe adverse effects in patients diagnosed with breast and esophageal cancer[225,226]. Notably, neoadjuvant combined immunotherapy and chemotherapy produced better outcomes without more adverse effects compared to chemotherapy[225]. Furthermore, bispecific T cell-based approaches have been reported to increase the efficacy of some drugs in drug-resistant cancers, such as pancreatic cancer, representing a novel treatment for MDR cancer cells[227]. Due to the toxic effects produced by ABC transporter inhibitors, immunotherapy may represent an approach that produces better tolerance and immune checkpoint inhibitors currently undergoing evaluation (e.g., PD-1 and CTLA-4) may further increase the use of this approach in overcoming MDR[228].

The targeting of MDR-mediated mechanisms independent of ABC transporters is also being investigated, including the use of BBB-disrupting compounds, ultrasound-mediated delivery, and peptide-drug conjugates. The disruption of the permeability of the BBB to increase the concentration of chemotherapeutic compounds can be achieved by osmotic disruption with intra-arterial drug administration, intrathecal/intraventricular administration, laser interstitial thermal therapy, convection-enhanced delivery, and ultrasound methods[229].

Conclusion

The role of ABC transporters in normal tissues is vital and has been validated by numerous studies. The complexity of the BBB and the expression of ABC transporters can significantly limit the efficacy of anticancer drugs used in the treatment of different types of brain tumors. ABCB1 and ABCG2 transporters are the main ABC transporters that are expressed in the BBB in cancerous tumors. Despite the increased permeability of the BBB due to brain tumors, the ABCB1 and ABCG2 transporters can significantly decrease the accumulation of anticancer drugs in the brain and result in treatment failure and relapse.

The ABC inhibitors that were developed failed to be clinically approved for the following reasons: 1) a lack of efficacy in clinical studies, resulting from insufficient levels to produce an efficacious response; 2) significant adverse effects and toxicities and 3) unsuitable pharmacokinetic profiles. Thus, there is an urgent need to use advanced or novel strategies to overcome anticancer drug resistance in brain tumors, such as PDT, nanomedicine, RNAi, and CRISPR/Cas9 gene editing. Furthermore, the development of new compounds with broader ABC transporter inhibitory efficacy could represent another approach by developing drugs that effectively target more than one transporter, such as dual inhibitors of ABCB1 and ABCG2 transporters or by combining drugs that efficaciously inhibit these transporters.

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