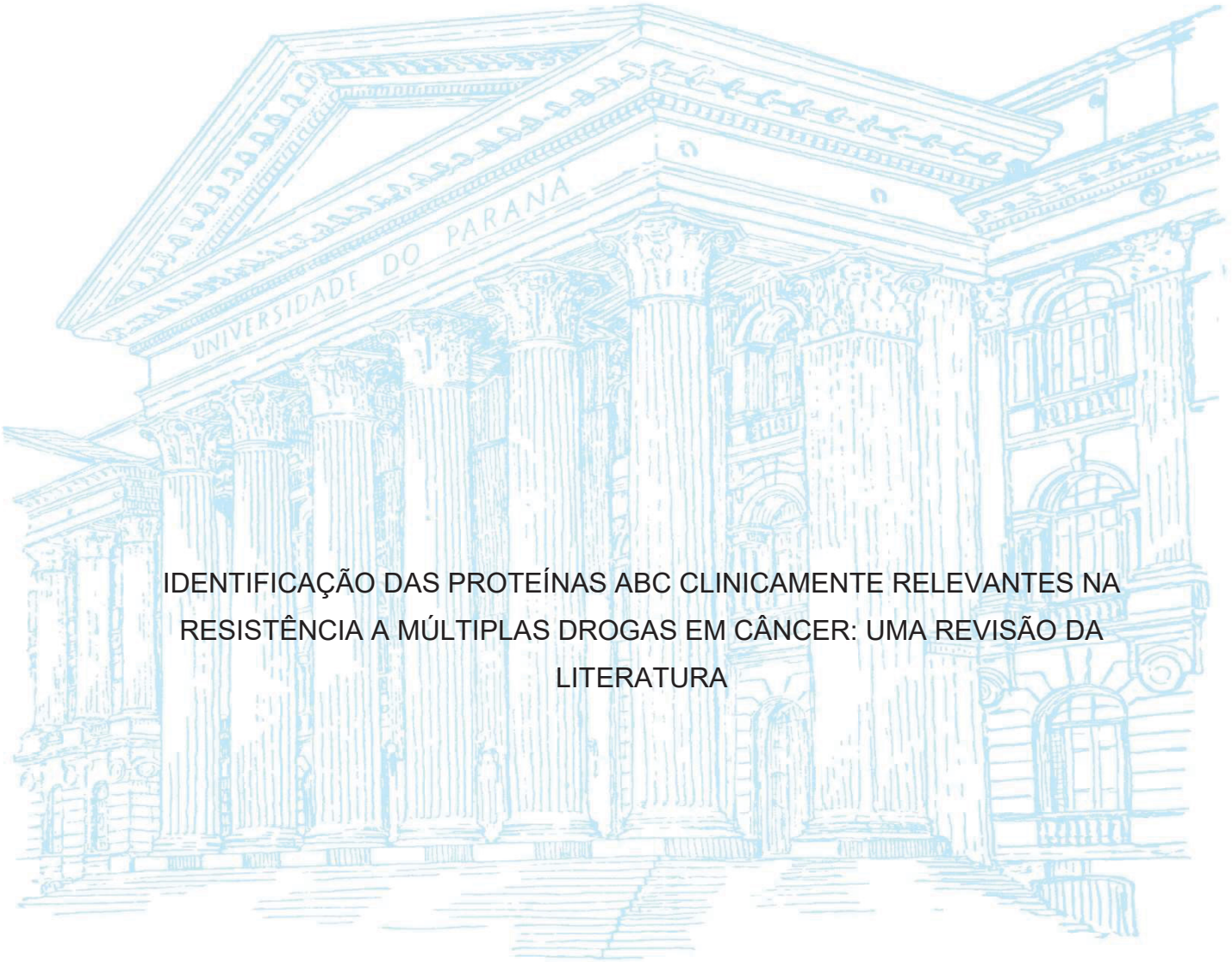
UNIVERSIDADE FEDERAL DO PARANÁ

ANDREZZA VIVIANY LOURENÇO MARQUES



IDENTIFICAÇÃO DAS PROTEÍNAS ABC CLINICAMENTE RELEVANTES NA RESISTÊNCIA A MÚLTIPLAS DROGAS EM CÂNCER: UMA REVISÃO DA LITERATURA

CURITIBA

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Tese apresentada ao curso de Pós-Graduação em Ciências Farmacêuticas, Setor de Ciências da Saúde, Universidade Federal do Paraná, como requisito parcial à obtenção do título de Doutor em Ciências Farmacêuticas.

Orientador: Prof. Dr. Glaucio Valdameri

Coorientadora: Profa. Dra. Vivian Rotuno Moure Valdameri

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Os membros da Banca Examinadora designada pelo Colegiado do Programa de Pós-Graduação CIÊNCIAS FARMACÊUTICAS da Universidade Federal do Paraná foram convocados para realizar a arguição da tese de Doutorado de **ANDREZZA VIVIANY LOURENCO MARQUES** intitulada: **Identificação das proteínas ABC clinicamente relevantes na resistência a múltiplas drogas em câncer: uma revisão da literatura**, sob orientação do Prof. Dr. GLAUCIO VALDAMERI, que após terem inquirido a aluna e realizada a avaliação do trabalho, são de parecer pela sua Aprovação no rito de defesa.

A outorga do título de doutora está sujeita à homologação pelo colegiado, ao atendimento de todas as indicações e correções solicitadas pela banca e ao pleno atendimento das demandas regimentais do Programa de Pós-Graduação.

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“Para adquirir conhecimento é preciso estudar; mas para adquirir sabedoria, é preciso observar.”

Marilyn Vos Savant.

RESUMO

O câncer é a segunda principal causa de morte no mundo e seu crescimento global permanece contínuo. Uma das principais causas de mortalidade por câncer é a resistência a múltiplas drogas (MDR). A MDR no câncer está associada à superexpressão de proteínas ABC, responsáveis pelo efluxo de quimioterápicos antineoplásicos, diminuindo a concentração intracelular das drogas e desencadeando o fenótipo de MDR. O genoma humano codifica 48 proteínas ABC, sendo a maioria delas transportadores de membrana. Apesar da relevância clínica dos três transportadores ABC: glicoproteína P, MRP1 e ABCG2, não há consenso sobre o número exato de proteínas ABC responsáveis pela MDR. Com base em referências públicas de diferentes bancos de dados, foi investigada a associação da superexpressão das 48 proteínas ABC com o fenótipo MDR em câncer. O objetivo deste estudo foi criar um painel contendo as principais proteínas ABC clinicamente relevantes para serem usadas em futuros estudos clínicos para entender melhor o papel das proteínas ABC na MDR no câncer. Esta revisão da literatura avaliou os artigos que descrevem a superexpressão de proteínas ABC relacionadas ao fenótipo MDR. Foram considerados elegíveis nesta pesquisa os estudos *in vitro* e clínicos publicados até 2022. No entanto, para ser inclusa neste painel como proteína ABC clinicamente relevante, a proteína ABC deveria atender aos três seguintes critérios: (1) pelo menos 2 estudos contendo um agente quimioterápico descrito como substrato ou associado a resistência; (2) pelo menos 2 estudos mostrando superexpressão em amostras de câncer - estudos clínicos e (3) pelo menos 2 estudos mostrando superexpressão em linhagens celulares de câncer - estudos *in vitro*. De acordo com os critérios estabelecidos foram identificadas 20 proteínas ABC relacionadas com MDR em câncer. Adicionalmente foi possível identificar os principais quimioterápicos antineoplásicos relacionados com a MDR em câncer e as neoplasias mais prevalentes associadas à superexpressão de proteínas ABC. Por fim, também foi avaliado um panorama das neoplasias que associam em seus protocolos de tratamento quimioterápicos antineoplásicos que são substratos da glicoproteína P, MRP1 e ABCG2, e que, portanto, estão envolvidos diretamente na MDR em câncer.

Palavras-chave: câncer; resistência a múltiplas drogas; transportadores ABC; quimioterapia; antineoplásicos.

ABSTRACT

Cancer is the second leading cause of death worldwide and, its global growth remains continuous. One of the major causes of cancer mortality is the multidrug resistance (MDR). MDR in cancer is associated with the overexpression of ABC proteins, responsible for the efflux of antineoplastic chemotherapeutic drugs, decreasing the intracellular concentration of drugs and triggering the MDR phenotype. The human genome encodes 48 ABC proteins, most of them ABC transporters. Despite the clinical relevance of the three ABC transporters: P-glycoprotein, MRP1 and ABCG2, there is no consensus about the exact number of the ABC proteins responsible for the MDR. Based on public data from different database, it was investigated the association of the overexpression of the 48 ABC proteins with the MDR phenotype in cancer. The goal of this study was to create a panel containing the main clinically relevant ABC proteins to be used in future clinical studies to better understand the role of ABC proteins in MDR in cancer. This review was based on articles describing the overexpression of ABC proteins related to MDR phenotype. *In vitro* and clinical studies published up to 2022 were eligible. However, to be included in this panel as a clinically relevant ABC protein, the protein should meet the three following criteria: (1) at least 2 studies containing a chemotherapeutic agent described as a substrate or associated with resistance; (2) at least 2 studies showing overexpression in cancer samples - clinical studies and (3) at least 2 studies showing overexpression in cancer cell lines - *in vitro* studies. In this study it was identified 20 ABC proteins related with MDR in cancer. According to these criteria, 20 ABC proteins related to MDR in cancer were identified. Additionally, it was possible to identify the main antineoplastic chemotherapy drugs related to MDR in cancer and the most prevalent neoplasms associated with the overexpression of ABC proteins. Finally, it was evaluated the different cancer types treated with antineoplastic chemotherapy that are substrates of P-glycoprotein, MRP1 and ABCG2, and which, therefore, are directly involved in MDR in cancer.

Keywords: cancer; multiple drug resistance; ABC transporters; chemotherapy; antineoplastics.

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ABC	-	ATP *binding cassette*
ATP	-	*Adenosine Triphosphate*
MDR	-	*Multidrug-resistance*
NBD	-	*Nucleotide Binding Domain*
TMD	-	*Transmembrane Domain*
MRP	-	*Multidrug Resistance-associated Protein*
ALL	-	*Acute Lymphoblastic Leukemia*
TAP	-	*Transporter Associated with Antigen Processing*
NCI	-	*National Cancer Institute*
INCA	-	Instituto Nacional de Câncer
FeS	-	*Iron-sulfur-cluster*
RNase-L	-	*Ribonuclease-L*
DNA	-	*Dexoxyribonucleic Acid*
mRNA	-	*Messenger Ribonucleic Acid*
HCC	-	*Hepatocellular Carcinoma*
BCRP	-	*Breast Cancer Resistance Protein*
MXR	-	*Mitoxantrone Resistant Protein*
ABCP	-	*Placenta-specific ABC*
FAC	-	*Fluorouracil, Doxorubicin, Cyclofosfamide*
FEC	-	*Fluorouracil, Epirubicin, Cyclofosfamide*
FDA	-	*Food and Drug Administration*
NCCN	-	*National Comprehensive Cancer Network*
ESMO	-	*European Society for Medical Oncology*
CALGB	-	*Cancer and Leukemia Group B*
CVAD	-	*Cyclophosphamide, vincristine, doxorubicin, dexamethasone*
AML	-	*Acute Myeloid Leukemia*
COG	-	*Children's Oncology Group*
SCLC	-	*Small cell lung cancer*
NSCLC	-	*Non-small cell lung cancer*
ChIP-seq	-	*Chromatin Immunoprecipitation Sequencing*
Co-IP	-	*Co-Immunoprecipitation*
CVA	-	*Cell Viability Assay*
ELISA	-	*Enzyme-linked immunoassay*
FC	-	*Flow cytometry*
FISH	-	*Fluorescence In Situ Hybridization*
HPLC-MS	-	*High-performance liquid chromatography/mass spectrometry*
ICC	-	*Immunocytochemistry of cultured cells*
ICP/MS	-	*Inductively coupled plasma mass spectrometry*
IF	-	*Immunofluorescence*
IHC	-	*Immunohistochemistry*
Micro-WB	-	*Micro-Western Blot*
PCR	-	*Polymerase chain reaction*
MS/MS	-	*Tandem mass spectrometry*
LC-MS/MS	-	*Liquid chromatography tandem mass spectrometry*
LC-UV	-	*Liquid chromatography interfaced to ultraviolet detection*
LSC	-	*Liquid scintillation counting*
RIP	-	*RNA immunoprecipitation*
qPCR	-	*Quantitative real-time Polymerase Chain Reaction*

RNA-seq	-	*RNA Sequencing*
RT-PCR	-	*Reverse-transcription polymerase chain reaction*
WB	-	*Western Blot*

SUMÁRIO

1. INTRODUÇÃO

O câncer se refere a um grande grupo de doenças que possuem em comum o crescimento e disseminação descontrolados de células anormais causando diferentes tipos de tumores sólidos e hematológicos (WHO, 2020). As células cancerosas são malignas e espalham-se através dos tecidos, podendo também invadir tecidos e órgãos adjacentes. Estas células podem, portanto, não responder aos mecanismos normais de controle do crescimento celular, assim como aos processos relacionados à morte celular programada (NCI, 2021a).

De acordo com a Agência Internacional de Pesquisa em Câncer (IARC), entre 2020 e 2025 são estimadas 10 milhões de mortes por câncer em ambos os sexos no mundo. Ainda, até o ano de 2040 o IARC estima um aumento de mais de 60% na mortalidade mundial relacionada ao câncer para ambos os sexos. Em relação à incidência, os dados mais recentes apontam que ocorreram cerca de 19.3 milhões de novos casos no mundo em 2020, com um aumento estimado deste número em 56% até o ano de 2040 (IARC, 2023).

No Brasil, cerca de 704.000 novos casos de câncer são estimados para o triênio de 2023 a 2025 (MINISTÉRIO DA SAÚDE, 2022). Destes, 483.000 consistem em novos casos, excetuando-se o câncer de pele não melanoma, que corresponde a 220.000 novos casos. Considerando a incidência por gênero, mama e próstata continuam a ser os tipos de câncer mais frequentes em mulheres e homens, respectivamente, correspondendo a 74.000 novos casos em mama e 72.000 de próstata (MINISTÉRIO DA SAÚDE, 2022).

As modalidades de tratamento do câncer incluem cirurgia, radioterapia, quimioterapia, terapia alvo molecular, imunoterapia e tratamento hormonal, além do transplante de células-tronco e medicina de precisão e a indicação de uma destas modalidades ou da associação delas irá depender do tipo tumoral e da fase ou estágio em que a doença se encontra (NCI, 2021b).

Em se tratando dos mecanismos de desenvolvimento do câncer, diferentes processos levam uma célula normal a transformações responsáveis pelo surgimento de células neoplásicas (RENAN et al., 1993). Características funcionais e habilitantes são descritas e propostas como condições essenciais ao processo de formação tumoral das células (HANAHAN; WEINBERG, 2000). A sinalização proliferativa, o potencial replicativo, a apoptose, as disfunções dos supressores tumorais, a

reprogramação do metabolismo celular, a angiogênese, evasão ao sistema imune e a metástase correspondem a mecanismos já compreendidos e bem estabelecidos que podem desencadear e suportar o processo tumoral (HANAHAN; WEINBERG, 2000, 2011). Sendo assim, a busca contínua pelo entendimento do câncer, em toda sua complexidade, possibilitou o aprimoramento das capacidades funcionais e adquiridas que promovem o surgimento e a progressão tumoral por meio de outros mecanismos além daqueles já existentes (HANAHAN, 2022). Foram propostos recentemente o desbloqueio da plasticidade fenotípica, a reprogramação epigenética não mutacional, os microbiomas polimórficos e a senescência celular como fatores contribuintes ao desenvolvimento e progressão do câncer (HANAHAN, 2022).

No que diz respeito ao tratamento farmacológico do câncer, mesmo com a disponibilidade de medicamentos quimioterápicos antineoplásicos, pertencentes a diferentes classes terapêuticas e com diferentes mecanismos de ação, a resistência ao tratamento medicamentoso ainda é um fator de desafio clínico (GILLET; EFFERTH; REMACLE, 2007). Uma das mais importantes causas da falha aos tratamentos quimioterápicos contra o câncer está associada ao fenômeno de resistência a múltiplas drogas, também conhecida como MDR (MURIITHI et al., 2020). A resistência às múltiplas drogas pode ocorrer através de duas vias distintas: 1) A resistência natural, que está relacionada a fatores intrínsecos do indivíduo e que pode ocorrer, portanto, desde o início do tratamento. Deficiência enzimática e instabilidade cromossômica são exemplos de resistência natural envolvendo tratamentos oncológicos com os antineoplásicos 5-fluorouracil e paclitaxel, respectivamente (AZWAR et al., 2021). 2) A resistência adquirida, que está relacionada a alterações na célula tumoral e que pode ser induzida por diferentes fatores (GOTTESMAN, 2002; CHOI; YU, 2014).

A MDR pode envolver diferentes mecanismos celulares e moleculares (GOTTESMAN, 2002). Um destes mecanismos refere-se à diminuição da captação de fármacos. Outros mecanismos envolvem alterações celulares que interferem na ação citotóxica das drogas antineoplásicas, incluindo, por exemplo, a diminuição da apoptose, o aumento no reparo dos danos ao DNA, alterações no ciclo celular e no metabolismo dos fármacos (GOTTESMAN, 2002). Contudo, pode-se destacar que o principal mecanismo de MDR é devido ao efluxo dos medicamentos quimioterápicos antineoplásicos mediado por transportadores ABC (BORST et al., 2000; SZAKÁCS et al., 2006; FLETCHER et al., 2010, 2016; BEGICEVIC; FALASCA, 2017).

A alteração nos níveis de expressão de proteínas ABC é observada tanto em tumores malignos sólidos, quanto nos hematológicos, sendo os seus altos níveis de expressão associados à MDR em câncer e descritos em estudos envolvendo leucemias, tumores de mama, de ovário, de pulmão, de fígado e de pâncreas, por exemplo (EFFERTH et al., 2006; CHAPUY et al., 2008; CHEN et al., 2015; LI et al., 2019; SEBOROVA et al., 2019; WU et al., 2019; SERRANO-OVIEDO et al., 2020).

A MDR em câncer ocorre através do mecanismo de efluxo de quimioterápicos antineoplásicos para o exterior das células, em decorrência da elevação da expressão das proteínas ABC (MURIITHI et al., 2020).

A unidade funcional mínima que caracteriza as proteínas ABC como transportadores consiste em dois domínios transmembranas (TMDs) e dois domínios citoplasmáticos de ligação a nucleotídeos (NBDs) (TUSNÁDY et al., 2006; WEEN et al., 2015; ROBEY et al., 2018). Os TMDs reconhecem e transportam os diversos substratos e os NBDs utilizam a energia promovida através da ligação e hidrólise de ATP para realizar a translocação de moléculas para o exterior da célula (WIND; HOLEN, 2011; WEEN et al., 2015; BEGICEVIC; FALASCA, 2017). Sendo assim, a superexpressão das proteínas ABC, promove o transporte dos agentes antineoplásicos para fora da célula tumoral, reduzindo os níveis de acúmulo das drogas anticâncer no interior da célula, com consequente redução da resposta terapêutica (DEAN, 2009; MURIITHI et al., 2020).

A consequente redução da concentração intracelular dos agentes citotóxicos diminui a resposta terapêutica ao tratamento, causando o fenótipo de MDR (DANO, 1973). As proteínas ABC são majoritariamente encontradas na membrana plasmática, mas podem ser observadas em outras localizações celulares, incluindo mitocôndria, retículo endoplasmático, núcleo e outras organelas (SEBOROVA et al., 2019). Devido a sua ampla distribuição em diferentes tecidos, os transportadores ABC possuem uma grande variedade de funções fisiológicas, incluindo o transporte de substâncias, tais como os peptídeos, lipídeos e toxinas (WILKENS, 2015). Além disso, os transportadores ABC estão envolvidos na regulação do metabolismo celular e também apresentam papel importante nas etapas da farmacocinética (absorção, distribuição, metabolismo e excreção) de absorção, distribuição e excreção de compostos farmacológicos. (LANGMANN et al., 2003; SZAKÁCS et al., 2004; KARATAS et al., 2016).

A superexpressão de proteínas ABC é identificada e associada à MDR em câncer, nos estudos clínicos, por meio de análises técnicas comparativas entre amostras tumorais controles e amostras analisadas antes e após a exposição aos quimioterápicos antineoplásicos (PARK et al., 2006; HONORAT et al., 2008; LITVIAKOV et al., 2012; HLAVÁČ et al., 2013). No entanto a maioria dos estudos publicados associa a superexpressão das proteínas ABC à MDR em câncer através de estudos *in vitro* (GUO et al., 2003; GILLET et al., 2004; THEILE et al., 2011; OISO et al., 2014; CHEN et al., 2017).

1.1 JUSTIFICATIVA

Apesar da bem consolidada a associação entre a superexpressão de proteínas ABC em pacientes com câncer e a diminuição da resposta efetiva ao tratamento quimioterápico, as evidências existentes na literatura apontam lacunas relacionadas à identificação de quais são as principais proteínas ABC relacionados com a MDR em câncer e à identificação de quais dos quimioterápicos utilizados nos protocolos clínicos são substratos de transportadores ABC. Há também carência de informação relacionando a frequência da superexpressão de proteínas ABC aos tipos de câncer existentes.

Nesse contexto, este estudo considerou a necessidade de avaliar os dados da literatura considerando quais são os tipos de câncer mais susceptíveis à resistência mediada por proteínas ABC, quais são as proteínas ABC mais frequentemente associadas aos diferentes tipos de câncer e correlacionar os medicamentos quimioterápicos com cada uma das proteínas ABC.

1.2 Objetivo

Identificar um painel de proteínas ABC relacionadas com a MDR por meio de revisão da literatura das 48 proteínas ABC para seleção daquelas relacionadas com MDR, considerando-se as publicações descrevendo estudos *in vitro* e estudos clínicos.

1.2.1 Objetivos específicos

- Verificar a localização celular das proteínas ABC e correlacionar com o mecanismo de MDR;
- Identificar quais são os quimioterápicos mais susceptíveis ao transporte mediado por transportadores ABC;
- Identificar quais são os tipos de câncer mais susceptíveis a baixa resposta ao tratamento devido ao efluxo mediado por transportadores ABC;
- Propor um painel de proteínas ABC para nortear novos estudos clínicos relacionados com MDR, bem como uma possível otimização dos protocolos de tratamento.

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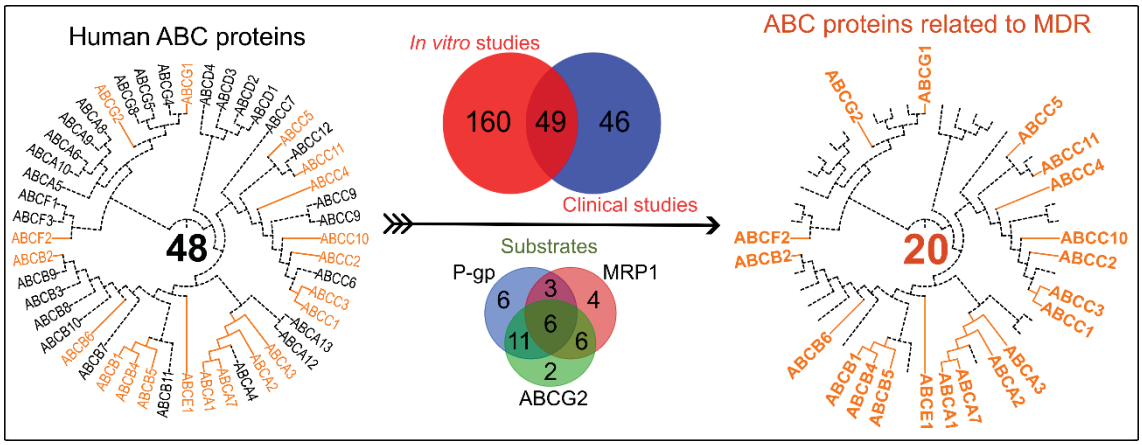
Graphical abstract



Highlights

- We identified 20 ABC proteins clinically related to multidrug resistance (MDR) in cancer. This panel can be used as a signature of MDR mediated by ABC proteins.
- 34 anticancer drugs were listed as substrates of the three most important ABC transporters: P-glycoprotein, MRP1 and ABCG2.
- Standard regimens used in the treatment of breast cancer, lung cancer and acute lymphoblastic leukemia (ALL) are highly subjected to MDR through ABC transporters.

A review of the 20 clinically relevant ABC proteins related to multidrug resistance in cancer

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Abstract

Cancer is the second leading cause of death from noncommunicable diseases in the world, mostly attributed to multidrug resistance (MDR) phenomenon by tumor cells. Overexpression of ATP-binding cassette (ABC) transporters is a major contributing factor resulting in MDR. Among the 48 ABC proteins encoded by the human genome, the overexpression of P-glycoprotein, MRP1 and ABCG2 are indubitably recognized as mediators of the efflux of diverse chemotherapeutics, thereby decreasing their intracellular concentration. However, other ABC proteins are also associated with MDR. Here, we revised the literature to identify the number of ABC proteins related to clinical manifestation of MDR in cancer, considering clinical and *in vitro* studies. A panel of 20 ABC proteins (ABCA1-3, 7, ABCB1, 2, 4-6, ABCC1-5, 10, 11, ABCE1, ABCF2, ABCG1, 2) was identified to be used as a MDR signature mediated by ABC proteins. Together with the classical MDR phenotype triggered by the drug efflux mediated by ABC transporters at the plasma membrane, this study also highlights the significance of drug sequestration into intracellular compartments mediated by ABC proteins. A total of 34 anticancer drugs were considered as substrate of at least one of the three most important ABC transporters, and the overlap of transport among P-gp, MRP1 and ABCG2 was presented. We further present that the common drugs used in standard regimens for mainly breast cancer, lung cancer and acute lymphoblastic leukemia (ALL) might be subjected to MDR through ABC transporters. Together with progressive advances in elucidating the mechanisms of MDR in cancer, these findings may help to design more efficient pharmacological treatment strategies to improve the objective response rate.

Keywords: Cancer; Multidrug resistance; ABC transporters; Anticancer drugs

1. Introduction: Multidrug resistance (MDR) in cancer and ABC transporters

According to the International Agency for Research on Cancer (IARC), in 2020 there were estimated 10 million cancer deaths worldwide and for the next 10 years it is estimated that cancer-related mortality will increase by approximately 30%. The most current data on cancer indicated a worldwide incidence of 19.3 million (18.1 million excluding nonmelanoma skin cancer) new cases and 10.1 million deaths in 2020 [1]. Data indicates that most of the mortality of cancer patients is caused by drug resistance [2].

Multidrug resistance, also known as MDR, is expressed through mechanisms that can promote concomitant functional and structural cellular changes, which cause resistance to different drugs. MDR in cancer can occur by two distinct pathways: (1) The

natural resistance which is related to personal intrinsic factors and it can occur as early as the beginning of treatment; (2) The acquired resistance, that is related to changes in tumor cells and it can be induced by a large range of different mechanisms [3–5]. The main mechanism conferring MDR is the increased efflux of drugs from cancer cells, thereby decreasing intracellular drug concentration, which is associate with the overexpression of ATP-binding cassette (ABC) proteins. ABC proteins are ubiquitously present, from prokaryotes to mammals, being recognized as cancer drug pumps for practically 50 years [6].

Most of ABC proteins are integral membrane proteins, built of characteristic domains, including transmembrane regions and cytoplasmic ATP-binding domains (Section 2), which in combination are responsible for ATP-driven translocation of several molecules, from here called substrates, across the plasma membrane. The function of human ABC transporters involves the efflux of several physiological structurally and biochemically unrelated compounds, such as lipids, bile salts, xenobiotics, nucleotides, organic anions and peptides [7]. ABC transporters are able to transport a large range of structurally unrelated chemotherapeutic drugs, thus, they are described as promiscuous transporters [8].

The substrates are expected to freely diffuse into the cells, and the ABC transporters may recognize them in the cytosol or into the plasma membrane to allow their translocation to the extracellular environment [9–11]. Among the human ABC transporters, three of them: P-glycoprotein (P-gp), MRP1 and ABCG2 have been widely related to poor patient outcomes in many different tumors, including hepatocellular carcinoma, colorectal cancer, breast cancer, lung cancer and leukemias (please refer to [12,13] for the most recent updates in the field). P-gp preferentially transports large hydrophobic molecules, while MRP1 and ABCG2 can transport both hydrophobic drugs and large anionic compounds, as drug conjugates [14]. Interestingly, an overlap of substrate recognition and transport mediated by these three ABC transporters, as observed by mitoxantrone and doxorubicin, hampers the association of MDR to a single ABC transporter [15–17]. Consequently, it remains challenging to predict effectively if one specific ABC protein is responsible or a combination of ABC proteins are implicated in the MDR phenomenon.

To highlight the importance of ABC proteins-driven MDR in cancer, we organize our discussion firstly presenting an overview of the main features of ABC proteins, followed by a brief summary of each ABC subfamily (Section 2). In Section 3, we define some selection criteria to deeply review the literature concerning the role of human ABC proteins in cancer. Table 1 lists the selected 20 ABC proteins related to MDR in cancer. In Section 4, we correlate the tabulated data to number of publications, number of

chemotherapeutic drugs involved in resistance and the type of cancer samples and cancer cell lines (*in vitro*) involved in the ABC proteins up-regulation. In Section 5, we discuss the chemotherapeutic drugs used in cancer treatment regimens that are substrates of P-gp, MRP1 and ABCG2 and the impact of this resistance prognosis. Concluding remarks are provided in Section 6.

2. Main features of ABC proteins

According to domain organizations and primary sequence homology, human genome encodes 48 ABC proteins (Figure 1A), which are distributed into seven subfamilies named from ABCA to ABCG. By definition, ABC proteins are composed by an ATP binding cassette, known as the nucleotide-binding domain (NBD). NBD contains conserved subdomains, including the Walker A and B motifs, the ABC signature motif (also called C) and the D, H and Q loops, which allow distinguishing among others ATP-driven pumps. To be further considered as ABC transporter, the protein also contains transmembrane domains (TMDs), composed of helices that participate in the substrate recognition and translocation [18–20].

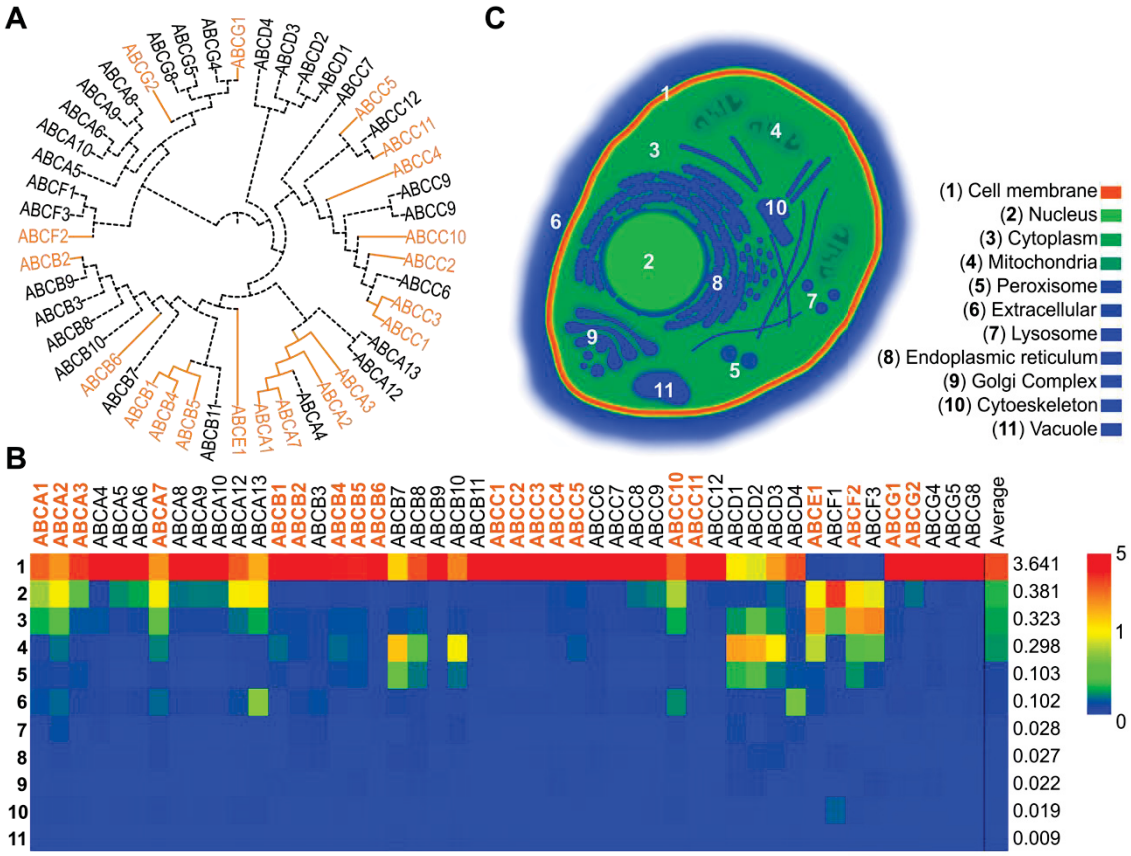

Figure 1: Phylogenetic tree and subcellular localization of human ABC proteins. (**A**) Phylogenetic tree. The amino acid sequences of 48 ABC proteins derived from Uniprot

database (https://www.uniprot.org) were aligned using Clustal Omega [21]. The neighbor-joining tree was constructed using the interactive tree of life webserver (iTOL) [22]. (**B**) Heatmap representing the subcellular localization of ABC proteins predicted by CELLO version 2.5 (http://cello.life.nctu.edu.tw/). (**C**) Schematic overview of the cell to represent the subcellular localization of the ABC proteins. Red color indicates higher presence of ABC proteins in the cell and blue color indicates its lower presence. The 20 clinically relevant ABC proteins found in this work are showed in orange.

All ABC transporters share a minimum core architecture consisting of four domains, two NBDs and two TMDs. Recent advances in structural determination of both ABCG2 and P-gp revealed details in the transport mechanism cycle and the polyspecific nature of their substrate binding sites [23,24]. In the absence of ligands, ABC transports are in the inward-facing conformation, in which the two NBDs are widely separated. Slightly conformational changes are induced by the substrate binding at TMDs, and the allosteric coupling for transport of the substrate across the plasma membrane occurs through three general steps: (1) Upon the binding of ATP, the two NBD dimerize, adopting a NBD closed configuration; (2) Conformational changes triggers the high substrate affinity in the inward-facing state to the low substrate affinity in a state called outward-facing conformation, which create a channel for substrate translocation; and (3) ATP hydrolysis and nucleotide release from the NBDs reset the protein structure [25,26].

Some members of ABCC family, represented by ABCC1-3, ABCC6 and ABCC8-10, have an additional TMD, creating a third domain named membrane-spanning domain (MSD0) that it is not related to the transport activity [27–29]. To ensure that this architecture functions as transporter, ABC transporters are classified in complete or half-transporters. Complete transporters consist of two NBD with conserved sequence motifs, Walker A and Walker B, separated by a sequence of 90 to 120 amino acids, and two TMD, such as ABCA members, ABCB1, ABCB4-5, ABCB11, ABCC4-5, ABCC7-9, ABCC11-12 [11,18,19]. The half-transporters are those that possess only one NBD and one TMD, and thus they require dimerization with similar transporters in order to have functionality, including, for instance, ABCB2, ABCB3, ABCB6-10, ABCD and ABCG families [11,18,19,30].

Most human ABC proteins are located on enterocytes, biliary hepatocytes, proximal tubules of kidney and the epithelium cells at blood-brain barrier, being pivotal players in both cellular homeostasis of endogenous compounds and protection against xenobiotics [31]. Therefore, the functionality of ABC proteins depends on their subcellular localization. ABC members besides being described on the surface cell membrane, have also been found in various intracellular organelles, which link to protein synthesis (endoplasmic reticulum – ER), posttranslational modification (Golgi apparatus), trafficking/recycling (Golgi and endosomes) and degradation (lysosomes), and even

mitochondria [32]. In this work, the subcellular localization of the 48 ABC proteins was predicted using the amino acid sequence derived from the UniProt database in the CELLO v2.5 [33]. To illustrate this, the generated data was tabulated and plotted as heatmaps (Fig. 1B and C).

From the seven subfamilies, the ABC transporters are members of five of them: ABCA, ABCB, ABCC, ABCD and ABCG, being located at plasma membrane and thus can translocate substrate to the extracellular environment. Therefore, is not surprising that members of these subfamilies, mainly including ABCA2, ABCB1, ABCB4, ABCB11, ABCC1-6, ABCC11, ABCC12 and ABCG2 are involved in drugs efflux and cancer MDR [34–36]. Since the subcellular localization prediction using CELLO is based on amino acid composition, the results do not necessarily reflect experimental data. For instance, although ABCD4, ABCA3, ABCB9 have been experimentally found in lysosomes [37], they were here primarily located at the plasma membrane (Fig. 1B). Two further subfamilies, ABCE and ABCF, lack TMDs and thus cannot be considered as transporters, being located in the cytoplasm and nucleus. Although the members of these subfamilies has been mainly involved in the regulation of protein synthesis and inflammatory processes, such as ABCE1 [38,39] and ABCF [40,41], their recent involvement in cancer has been poorly understood [42–45].

In order to understand the role of ABC proteins on MDR in cancer, the main features of each ABC subfamily are reviewed bellow.

2.1. ABCA

The ABCA subfamily includes 12 members, designated ABCA1-10, ABCA12 and ABCA13. This family has two subgroups, divided according to their chromosomal location and phylogenetic analysis. The phylogenetic analyses (Fig. 1A) supported the division of ABCA subfamily into two subgroups: the subgroup I comprising *A5, A6, A8, A9*, and *A10* (subgroup I) and the subgroup II comprising *A1, A2, A3, A4, A7, A12*, and *A13* [46]. In addition, *A5, A6, A8, A9*, and *A10* are located on the chromosome 17q24.3, while *ABCA1, A2, A3, A4, A7, A12*, and *A13* are located on six other different chromosomes [36].

In the ABCA subfamily, the typical structure consists of two TMDs composed by six membrane-spanning units each and two cytoplasmic regulatory domains. In addition, a unique characteristic of this subfamily is the presence of a large extracellular loop forming a domain between the 2 TMDs, with an unknown function [47,48]. Most of ABCA proteins are localized in the plasma membrane, where they are involved in the transport

of lipids, including cholesterol [49,50]. Some of them can be found in the cytoplasm [51], lysosome [52], endosome [52] and Golgi apparatus [53].

Mutations in ABCA genes have been identified as the origin of some serious disorders associated with lipid transport. For instance, mutations in *ABCA1* can lead to severe deficiency syndromes, including Tangier diseases [54], while mutations in *ABCA12* has been associated with disorders on the transport of extracellular epidermal lipids, which is related to the pathogenesis of Harlequin ichthyosis [55]. In addition, mutations in *ABCA3* has been related to a surfactant deficiency which can lead to lethal respiratory diseases, especially in newborns [56].

Usually, an increase of ABCA protein levels is associated with drug resistance and worse outcomes in cancer treatments. It has been suggested that some ABCA members participate in the subcellular drug efflux, including drugs involved in cancer treatments, thus they seem to have an important role in chemoresistance [57–59]**.** Studies have demonstrated the overexpression of some ABCA members in different types of cancer, including leukemia [60], prostate [61], pancreas [62], ovarian [63], brain tumors [64] and others. Furthermore, it has been shown that this up-regulation reduce the intracellular accumulation and cytotoxicity of chemotherapy drugs, including mitoxantrone [65], doxorubicin [60] and paclitaxel [62]. In addition, other chemotherapeutic agents, such as daunorubicin, etoposide, vincristine, cytarabine [66], cisplatin [67,68] and imatinib [69] are also related with the resistance mediated by some ABCA transporters.

Interestingly, the lysosomal localization of ABCA3 is related to its function of intracellular drug sequestration, which further contributes to MDR in cancer [66,69]. As lysosomal protein, ABCA3 orientation (as other lysosomal ABC proteins ABCB9 and ABCD4) comprises NBDs facing the cytoplasm, thereby leading to suggested function of exporter, transporting substrates from the cytoplasm to the lysosomes [66,69].

2.2. ABCB

The ABCB subfamily is one of the best known due to the presence of P-glycoprotein (P-gp), also called MDR1 transporter. This protein encoded by *ABCB1* gene is one of the most well-known and characterized transporters involved with MDR [24,70]. Chromosomal location is variable among the members of ABCB subfamily, for instance, *B1* and *B4* are located on 7q21.12 chromosomal region, while *B2, B5, B6, B8* and *B10* are located on chromosomes 6p21, 7p21.1, 2q35, 7q36.1 and 1q42.13, respectively [36].

The ABCB subfamily comprises 11 ABC transporters. Some members of this subfamily are also known as multidrug resistance protein (MDR) or transporter

associated with antigen processing (TAP). This is the only human subfamily to have both half and complete types of ABC transporters. Seven of these eleven transporters are classified as half-transporters, represented by B2, B3, B6-10. The others, B1, B4, B5 and B11 are complete ABC transporters [71]. ABCB1/P-gp/MDR1 is the archetype example of multidrug efflux pumps, a core structure of four domains, 2 TMDs and 2 NBDs that are fused together to active transport substrates [72].

The ABCB transporters are found in different subcellular location, including plasma membrane [73], cytoplasm [74,75], Golgi apparatus [75], endosome [76] and lysosome [76,77]. In addition to plasma membrane [78], P-gp is also localized in intracellular compartments, such as Golgi apparatus [79], ER [80] and cytoplasm [80]. ABCB6-8 and B10 has been considered as mitochondrial ABC transporters [81]. ABCB7, B8 and B10 are localized in the inner mitochondrial membrane, with NBD facing the matrix [82]. Although ABCB6 does not comprise a mitochondrial targeting domain [83], it has been described in outer mitochondrial membrane [84] and lysosomes [76]. ABCB9, in turns, is classified as a lysosomal protein [77].

ABCB transporters can perform different roles on cells. For instance, P-gp can have an important role on absorption and efflux of substrates, expelling harmful or cytotoxic compounds from the cells, protecting important tissues, such as blood-placenta, blood-testis and blood-brain barrier [85,86]. In addition, P-gp have a pivotal role on MDR in cancer, promoting the efflux of many cytotoxic drugs, such as docetaxel [87], doxorubicin [88] and topotecan [89].

P-gp localization in intracellular compartments might be implicated in the chemotherapeutic drugs sequestration, such as doxorubicin, daunorubicin and vinblastine [90]. ABCB4, on the other hand, can be found on the liver, specifically in the bile canicular membranes of hepatocytes, which involves phosphatidylcholine transport and on the transport of xenobiotics, especially those substances that might be toxic to the liver [91,92]. The location in outer mitochondrial membrane allows ABCB6 transporter to act as porphyrin metabolites importer [84], playing an essential role on heme biosynthesis and erythroid differentiation. *ABCB6* gene encodes the Langereis (Lan) blood group antigen, which is responsible for erythropoiesis [93]. The mitochondrial ABCB7 [94], B8 [95] and B10 [96] seems to protect the organelle to oxidative stress, and B10 also participates of heme biosynthesis through iron import [97].

Regarding mutations on *ABCB* members, mutations affecting *ABCB11* gene can be associated to the development of liver hereditary disorders, including progressive intrahepatic cholestasis (subtypes 2) [98] and intrahepatic cholestasis of pregnancy [99]. Genetic polymorphisms at *ABCB1* gene can influence pharmacokinetics of several chemotherapeutic agents, such as methotrexate [100] and afatinib [101]. P-gp can also

influence pharmacodynamics (disposition) and therapeutic response of a large range of drugs [102], interfering on efflux of docetaxel [103], including antivirals (Atazanavir [104]), calcium channel blockers (Nifedipine [105]), antiarrhythmics (digoxin [106]), antifungals and others [70].

There are several studies showing the ABCB family overexpression in tumor cells such osteosarcoma tumors [107], myeloma [88], colorectal [87], lung [108], breast [109] ovarian [110] and leukemias [111,112]. Further association of the up-regulation of ABCB family with the poor chemotherapy response due to efflux drugs was observed for taxanes [113], imatinib [111] and FEC protocol (5-fluorouracil, epirubicin and cyclophosphamide) [57].

2.3. ABCC

The ABCC subfamily, also known as the MRP (multidrug resistance-associated protein), comprises of 12 members. The chromosomal location is distinct among ABCC subfamily members. Excepting *C1* and *C6* (16q13.12), and *C11* and *C12* (16q12.1), which are located on chromosome 16, the others *ABCC* genes are located on specific chromosomes: *C2* on 10q24.2, *C3* on 17q21.33, *C4* on 13q32.1, *C5* on 3q27.1, *C7* on 7q31.31, *C8* on 11p15.1, *C9* on 12p12.1, *C10* on 6p21.1 and *C13* on 21q11.2 [36].

The ABCC subfamily is involved in the transport of a large number of anions and organic conjugates, such as sulfates, phosphates, glutathione and glutamate, and it is associated with the transport of several drugs [114]. The structural core classifies this family as complete transporters. ABCC4, C5, C7, C11 and C12 have 2 TMDs and 2 NBDs [71], whereas ABCC1-3, C6 and C8-10 besides 2 TMDs, also have a unique characteristic of the a third TMD at the N-terminal with unclear function [27–29].

The ABCC proteins are identified in different subcellular locations, including Golgi apparatus [115], endosomes [115,116], lysosome [117] and ER [118], being mostly located in the plasma membrane [116,119,120]. ABCC1 (MRP1) can also be found at outer mitochondrial membrane, suggesting that this transporter may have a role protecting the mitochondrial DNA from oxidative damage [121,122]. As lysosomal protein, MRP1 has been involved in drug sequestration, as observed by doxorubicin intracellular accumulation in vesicles, preventing its reach in the nucleus [117]. On the other hand, ABCC2 transporter functions as a canicular efflux pump, participating on physiological transport of organic anions, such as bilirubin glucuronide into the bile and on hepatobiliary excretion of some compounds, including drugs [123,124]. Although ABCC2 was found to be expressed in the plasma membrane, its involvement in cisplatin

resistance in ovarian carcinoma cells depends of higher levels in nuclear membrane, which is consistent to the target site of the chemotherapy drug [125].

Many studies have shown the relationship between ABCC up-regulation and chemoresistance in cancer, as a consequence of the drug efflux. The list of ABCC substrates include doxorubicin [126], paclitaxel [127,128], gemcitabine [129] and platinum-containing drugs, such as cisplatin, carboplatin and oxaliplatin [110,130]. The MDR mediated by ABCC transporters can be observed in a large range of tumors [125,131–134], such as glioma [135], hepatocellular carcinoma [136], breast [57,109,137], ovarian [32] and prostate [138]. Further, MRP1 is reported to be overexpressed in colorectal adenocarcinoma, especially in those tumor tissues that were resistant to oxaliplatin [139] and the overexpression of ABCC4 in retinoblastoma is reported as the main cause of resistance to chemotherapeutic agents [140]. In addition, polymorphisms in *ABCC1* gene influence hematological toxicity of drugs such as fluorouracil, epirubicin and cyclophosphamide [141].

2.4. ABCD

The ABCD family consists of 4 members represented by *ABCD1* (ALD), *D2* (ALDL1 or ALDR), *D3* (PXMP1 or PMP70) and *D4* (PMP69 or P70R). *ABCD1-4* are located on chromosome regions Xq28, 12q11, 1p22.1, 14q24.3, respectively [36]. All of these genes encode half-transporters, which contain one TMD and one NBD. To become functional for the transport of long chain fatty acids, these half-transporters need to form homo or heterodimers [142,143]. With respect to subcellular localization, ABCD proteins are mostly located in the peroxisomal membrane, including *ABCD1-3* [144,145]. *ABCD1* is also found in ER, mitochondria and lysosome [146], while *ABCD4* is not found in peroxisome and it can be found in ER and lysosome [147]. Current knowledge classifies *ABCD4* as lysosomal protein responsible for the transport of cobalamin from the lysosomes to the cytosol, which can be assumed as reverse transport, since NBDs dimer facing cytosol [148].

ABCD proteins are mainly involved in lipid and vitamin disorders, including hereditary adrenoleukodystrophy, which seems to be related to the gene *ABCD2* [149]. Very little is known about the role of ABCD family in cancer. *ABCD2-4* were down-regulated, while *D1* was up-regulated in breast carcinoma tumors. Further investigation with this ABCD family is needed to identify chemotherapeutic drugs as substrates [142].

2.5. ABCE

The ABCE subfamily is represented by its unique member, ABCE1. *ABCE1* is located on the chromosome 4q31 [36] and is the most highly conserved in all eukaryote (identity over 90%) and archaea genome (but is not found in bacteria), suggesting a common function in these organisms [150,151].

ABCE1 protein structure consists of four domains encoded in one polypeptide chain: that is two NBDs that face each other in a head-to-tail orientation, which is mediated by the hinge domain at the C-terminus of the protein, and the N-terminus contains the iron-sulfur-cluster (FeS) domain [152]. ABCE1 was initially described as ribonuclease L (RNase L) inhibitor through binding of its FeS cluster [38,153]. By inhibiting intracellular RNase L activity, ABCE1 limits host response to viral infection [38]. Despite of this nonessential function, because of the unique presence of FeS cluster, ABCE1 protein is expected to be involved in a diverse cellular functions, including mitochondrial respiratory pathways, ribosome assembly, translation of proteins, regulation of DNA metabolism and cellular proliferation and apoptosis [38,154]. Whereas ABCE1 essentially involved ribosome recycling and mRNA translation [155–157] it also participates of cell proliferation [158], iron homeostasis and oxidative stress [159]. This protein has not the same structure as other proteins of ABC family due to the lack of TMD. This means that ABCE1 has no ABC transmembrane transport activities and is so-called simply as ATPase. However, in *Caenorhabditis elegans* ABCE1 affects the transport of proteins to the nucleus and mRNA in opposite direction through unclear mechanism [160].

The subcellular location of ABCE1 protein is in the cytoplasm and mitochondria [161]. In normal tissues, ABCE1 can be found on brain, kidney, lung, liver, spleen, heart and pancreas [162]. Despite of its unique structural features, the overexpression of ABCE1 has been associated with cancer cells and chemotherapy treatments response. *ABCE1* was up-regulated in some tumor tissues, including breast, colorectal, lung [163], glioma [164] and hepatocellular carcinomas [44]. This overexpression might be a useful marker to tumor progression and metastasis in lung [165,166], colorectal cancer [167] and hepatocellular carcinoma [44]. Since the chemoresistance limits the treatment of advanced lung cancer patients [168–170], it is worth to mention that ABCE1 can affect the sensitivity of lung cancer cells to chemotherapeutic drugs, such as fluorouracil [171] and doxorubicin [163]. Furthermore, ABCE1 can affect the sensitivity of glioma cells to temozolomide [164]. If the mammals functionally evolved ABCE1 to mediate all these effects in cancer through RNase L inhibition, it remains to be elucidated. It is more likely that its possible function as nucleocytoplasmatic transporter plays a role in chemotherapeutics resistance [160]. Still, it can be assumed that this role is not related to the extracellular export of the substrates.

2.6. ABCF

The ABCF subfamily comprises three members, ABCF1-3, encoded by the genes located on chromosome regions 6p21.1, 7q36.1 and 3q27.1, respectively [36]. These three proteins have, as well ABCE1, a distinct structure from other members of ABC transporter family. ABCF1-3 are characterized by a pair of NBDs, but they lack the TMDs [172]. This structural feature predicts that ABCF members do not participates in the substrate transport across cellular membranes. In fact, the subcellular location of these proteins is predominantly in the cytoplasm but they can also be found in the nucleus [40].

Unlike ABCE1, ABCF proteins are present in the eukaryotes and bacteria, being involved in ribosome assembly, mRNA translation and antibiotic resistance [173]. Among the ABCF family members, F1 is most extensively characterized in eukaryotes. ABCF1 is also termed as ABC50 (GNC20 in yeast) and interacts through its N-terminal region with eIF2 (eukaryotic initiation factor 2), a protein that plays a key role in translation initiation and ribosomes biogenesis [174,175]. Human ABCF1 also plays a role in the regulation of transcription and stem-cell pluripotency through interaction with transcription factors OCT4 and SOX2 [175], and regulation of innate response possibly through interaction with Toll-like receptors [176]. ABCF1 is the only ABC protein part of a six-gene signature derived from mouse models which can be used to predict breast cancer patient survival [177]. Chemoresistance to 5-fluorouracil, doxorubicin and cisplatin was related to the overexpression of ABCF1 in hepatocellular carcinoma (HCC) cells [45]. Unexpectedly, the HCC cells stably overexpressing ABCF1 were able to translocate this protein to the plasma membrane, leading to efflux of doxorubicin, without significant association with expression of other ABC transporters. The impaired presence of ABCF1 at the cellular surface should involve its interaction with proteoglycans in plasma membrane [45]. Nevertheless, these results open a new avenue to investigate ABC proteins unclassified as transporters.

The lack of transmembrane domains probably indicates that ABCF2 is not related to transport activities of ABC superfamily, but it plays a role in the protein synthesis process associated with ribosomes [172]. Nevertheless, it is important to consider that some studies have shown the overexpression of ABCF2 protein in cancer tumor cells such as ovarian [178–180], cervical [178,181] and breast cancer [182] and its involvement in chemotherapy response. In ovarian and cervical tumors, the authors evaluated ABCF2 protein and the results showed its overexpression, although some factors such as clinical stage, histologic type, age or chemotherapy response did not seem to be significant [178,179,181]. Studies involving chemotherapy resistance had

indicated that ABCF2 overexpression might be related to platinum-derived drugs resistance in ovarian and gastric cancer cells [183]. ABCF2 was found to be up-regulated in breast carcinoma tissue after treatment when compared to normal tissues and the overexpression of ABCF2 in breast tumor cells might be involved in tumor growth suppression, especially at distant metastatic sites [109,182]. Furthermore, ABCF2 is also overexpressed at melanoma cells, especially in metastatic melanoma cells. This can be correlated to antiapoptotic potential and it can be associated to tumor progression and resistance to antineoplastic agents [43].

2.7. ABCG

The ABCG subfamily is composed of five half-transporters, ABCG1, G2, G4, G5, and G8 [184], encoded by *ABCG* genes located on distinct chromosomal regions. For instance, *ABCG1, G2* and *G4* are located on chromosomes 21q22.3, 4q22 and 11q23, respectively. Only *G5* and *G8* are located on the same chromosomal region, 2p21 [36].

ABCG proteins have one TMD and one NBD, and thus requires dimerization to form either homodimeric or heterodimeric structures in order to perform their activities as transporters [11,30,185–187]. Although ABCG2 forms functional homodimer in cultured cell in the absence of other ABCG member, the possibility to form heterodimer *in vivo* is expected [188], G5 and G8 are obligate heterodimer in order to be function at the cell membrane [189]. Additionally at plasma membrane [190–192], ABCG transporters have been identified in different subcellular locations, including mitochondria [193], ER [194] and Golgi apparatus [194]. Likewise other members of ABC superfamily, ABCG members are physiologically involved in lipid/sterol transport, mainly in liver and intestine [195].

The involvement of ABCG1, G4, G5 and G8 with MDR in cancer is far unknown. ABCG1 appears to play a role in the tumor microenvironment and its absence can result in cholesterol increasing and in development of inflammatory reactions as a consequence of mechanisms of cancer control [196]. It has been overexpressed in breast [109] and pancreatic [197] cancers. ABCG4 is a member closely related to G1, sharing amino acid sequence identity of 69% [198]. Although its physiological role in humans remains unclear, its overexpression was reported in non-small-cell lung cancer and associated with cisplatin resistance [199]. Mutations in either *G5* or *G8* genes cause sitosterolemia, which is characterized by the accumulation of sterols in plasma and tissues [200]. A variant D19H in ABCG8 is associated with gallstone disease [201], which, in turn, is associated with increased gallbladder cancer susceptibility [202].

The main ABCG member related to MDR in cancer is ABCG2 [12]. ABCG2 is also known as breast cancer resistance protein (BCRP), mitoxantrone resistant protein (MXR) and placenta-specific ABC transporter (ABCP). ABCG2 physiologically functions as a part of a self-defense mechanism, decreasing absorption of its substrates, like hemes of erythrocytes and stem cells enhancing their elimination [203]. Dysfunction of ABCG2 in normal cells is related to the transport of uric acid, leading to hyperuricemia. As consequence, this dysfunction can be involved on the process of gout, kidney disease and hypertension [204]. In addition to its presence in gastrointestinal and biliary tract, ABCG2 is a major component at the important barriers as blood-brain, placental, and blood-testis confers protection to the exposure to xenobiotics and harmful substances [205]. Thereby, ABCG2 is implicated in reducing systemic exposure to many drugs, including cimetidine [206], fluoroquinolone antibiotics [207], antiretrovirals used for treating of human immunodeficiency virus (HIV) [208], rosuvastatin used for the treatment of hyperlipidemia [209] and several antineoplastic drugs [36,210]. In fact, the list of substrates as well as inhibitors counts more than 300 compounds [8,211]. Therefore, FDA now recommends screening of new molecular entities for their interaction (inhibition or efflux) with ABCG2 to avoid drug-drug interactions [212,213].

At the clinics, overexpression of ABCG2 in tumor cells confers cancer MDR to a variety of anticancer agents. ABCG2 is overexpressed in malignant hematopoietic and lymphoid cells, as well on stem cells in leukemias and the drugs used to treat these cancers are substrates for ABCG2: fludarabine, flavopiridol, 6-mercaptopurine, methotrexate, dasatinib and danusertib (reviewed by Natarajan and colleagues [214]). ABCG2 overexpression has also been reported in a variety of solid tumors, including breast [137,215–221], colorectal [222–225], pancreas [197,226] and small-cell lung cancer [227], associated with resistance to docetaxel [137], FAC (Fluorouracil + Doxorubicin + Cyclophosphamide) [137,217,220] and FEC (Fluorouracil + Epirubicin + Cyclophosphamide) [217,220].

3. Identification of the clinically relevant ABC proteins related to MDR in cancer

According to Gottesman and colleagues (2016), preclinical experiments do not reproduce the models of drug resistance linked to increased gene expression as observed in clinical tumor samples. Although there is no single resistance mechanism in predicting chemotherapy failure, the overexpression of ABC proteins in tumor samples has been well-related to MDR [9].

To date, out of 48 known human ABC proteins: about 24 of them could be overexpressed in tumor cell lines under selective pressure, leading to *in vitro* acquired

MDR [228]; 20 can transport chemotherapy drugs (ABCA1-3, ABCA8, ABCB1, ABCB4-5, ABCB8, ABCB11, ABCC1-6, ABCC10, ABCC11, ABCE1, ABCG1 and ABCG2) [11]; ABCB1, ABCB5, ABCC1, ABCC4 and ABCG2 have been associated to intrinsic resistance of cancer stem cells [8,229]; as reviewed by Ween et al. 2015 [11], up-regulation of ABC proteins expression in human malignant tissues was observed for most of the ABC proteins (exceptions includes ABCA5, ABCA7, ABCB7-10 and ABCC9); evident association with clinical MDR and, consequently poor treatment response, which involves increased expression of ABC proteins following chemotherapy was observed for at least 10: ABCA1, ABCA3, ABCA12, ABCB1, ABCB5, ABCC1, ABCC2, ABCC5, ABCF2 and ABCG2 [11,57,60,230].

Among all, P-gp is the most studied ABC protein in MDR, followed by MRP1 and ABCG2. Certain cancers, including lung, kidney, colon and hepatocellular, have increased constitutive P-gp expression [231], while several others solid tumors and leukemia have induced expression of P-gp following chemotherapy [232]. Thus, several P-gp inhibitors (molecules that inhibit substrate efflux) have been developed to overcome drug resistance. Despite enormous advances in this field (please refer [233–235] for the most recent updates), the overall approach for the use of P-gp inhibitors failed in clinical trials [13,234]. The early generation of P-gp inhibitors led to toxicity [236]. The latest third generation, including Tariquidar (XR9576) [103,237,238], Zosuquidar (LY335979) [239] and Elacridar [240], although demonstrated tolerable side effects, did not improved anticancer efficacy compared to placebo group, suggesting that P-gp as a single target is not enough to circumvent MDR in cancer. This finding raised some point to improve the next clinical trials, such as: (1) the P-gp expression level may be monitored in patients' sample, which was not done in all clinical trials; (2) the overexpression of others ABC proteins that could replace the drug efflux may be also monitored and inhibited.

One major issue in this field is the extrapolation of *in vitro* experiments using tumor cell lines to clinical studies using human samples to determine the overexpression of ABC proteins in association with reduced sensibility to several chemotherapeutic drugs [241]. The methods to investigate gene and protein expression using cellular assays are sufficiently standardized. However, several challenges involve the acquisition of human specimens, especially for solid tumors, such as sampling achievement with full consent and in compliance with the ethical protocol, cell isolation (for bone narrow sample or peripheral blood), storage conditions (for instance, RNA stabilization solutions, liquid nitrogen, paraffin-embedded tissue blocks), limited number of cohort, determination of control group (normal tissue, before and after treatment) amount and quality of the mRNA obtained. Briefly, the detection of clinical MDR requires of molecular measurement of mRNA or protein levels, determination of subcellular localization, and

functional ability in transporting the chemotherapeutic drugs to the extracellular compartment [232,242–244].

Considering all these aspects, the goal of this review was to determine the minimum panel of ABC proteins expression pattern that should be investigated to effectively predict clinical MDR in response to chemotherapy in cancer. To orientate the study, a literature review of the 48 genes encoding ABC proteins related to MDR phenotype was performed, including *in vitro* and clinical studies published up to the last year, following these selection criteria: (1) at least 2 studies containing a chemotherapeutic agent described as a substrate or associated with resistance; (2) at least 2 studies showing overexpression in cancer samples - clinical studies and (3) at least 2 studies showing overexpression in cancer cell lines - *in vitro* studies. The results are shown in Table 1.

Table 1: Selection of ABC proteins considering their overexpression and relationship with MDR.

Gene	Anticancer drug related to MDR	Regimen	Neoplasia		Cell line	
			Type	Technique	Type	Technique
ABCA1	Cisplatin [68] Doxorubicin [245]	FEC (Fluorouracil + Epirubicin + Cyclophosphamide) / Paclitaxel + Trastuzumab [57] Paclitaxel + Carboplatin [63] ACT (Doxorubicin + Cyclophosphamide + Taxane) / TCHP (Docetaxel + Carboplatin + Trastuzumab + Pertuzumab) / TC (Docetaxel + Cyclophosphamide) [58]	Breast [57,58] Colorectal [59] Ovarian [63] Pancreas [197] Prostate [61]	IHC [58,63] Microarray [57,63] qPCR [59,61,63,197]	A2780, 27/87, SKOV3 (Ovarian) [63] HEK293T (Embryonic kidney), Caco2-ABCA1, DLD1-ABCA1 (Colorectal) [59] HepG2/DR (Hepatocellular carcinoma), MCF7/DR (Breast) [245] KCP-4 Cisplatin (Epidermoid carcinoma) [68] PC-3, DU145 (Prostate) [61]	ChIP [245] Co-IP [245] Confocal microscopy [59] CVA [61,68,245] ICP [68] IF [59] PCR [68] qPCR [59,63,68,245] WB [59,61,68,245]

ABCA2	Daunorubicin [36] Doxorrubicin [246] Estramustine [247] Methotrexate [246] Mitoxantrone [65] Paclitaxel [62] Vinblastine [246]	Consolidation: 6-Mercaptopurine + Cytarabine + Cyclophosphamide Protocol M: Methotrexate [248] Induction: Vincristine + Cytarabine + Daunorubicin + Etoposide [60] Induction: Vincristine + Doxorubicin + Asparaginase + Prednisone [248]	Acute lymphoblastic leukemia [246,248,249] Acute myeloid leukemia [60] Breast [109] Glioma [64] Hepatocellular carcinoma [136] Pancreas [62]	FC [248] IHC [62,64] Microarray [60,246] PCR [136] qPCR [60,64,109,246,248,249] WB [64,109]	GLC4-MITO (Lung-SCLC) [65] HL60/AR (Leukemia) [36] Jurkat/MTX+VBL+DOX-R (T-cell acute lymphoblastic leukemia) [246] Panc-02, Panc-02-PTX-R, SW1990 (Pancreas), HEK293T [62] SKEM-EM-R (Ovarian) [247] SK-Mel-147- Cisplatin (Melanoma) [250]	ChIP [250] CoIP [62] CVA [246,247] FISH [247] IF [247] Microarray [36,246] Northern blot [247] PCR [65,246,247] qPCR [36,250] Southern blot [247] WB [250]
ABCA3	Cisplatin [67,68] Cytarabine [60,66] Daunorubicin [66] Doxorubicin [60,246]	Consolidation: 6-Mercaptopurine + Cytarabine + Cyclophosphamide [248,251]	Acute lymphoblastic leukemia [246,248,249,251–253]	FC [66,69,248,251] FISH [69] ICC [69]	A549, NCI-H1650 (Lung-NSCLC) [67] CCRF-CEM /DOX+CYT+VBL+VCR+EPI-	Confocal microscopy [66] CVA [66–69,246] FC [66,67]

	Epirubicin [60] Etoposide [66] Imatinib [69] Methotrexate [246] Mitoxantrone [66] Paclitaxel [67] Vinblastine [60,246] Vincristine [60,66]	<u>Induction:</u> Vincristine + Doxorubicin + Asparaginase + Prednisone[248,251] <u>Induction:</u> Vincristine + Cytarabine + Daunorubicin + Etoposide [60] Paclitaxel / FEC (Fluorouracil + Epirubicin + Cyclophosphamide) [109] Protocol M: Methotrexate [248,251]	Acute myeloid leukemia [60,66] Breast [109] Chronic myeloid leukemia [69] Non-small cell lung cancer [67]	Immunohystochemistry [67,251] Microarray [60,246] qPCR [60,66,109,246,248,251–253] WB [66,109,253]	R (Acute myeloid leukemia) [60] CCRF-CEM/MTX+VBL+ DOX-R (T-cell acute lymphoblastic leukemia) [246] HEK293-ABCA3, ABCA3-eGFP (Leukemia) [66] Jurkat, DOX+CYT+VBL+VCR+EPI-R, K652, LAMA84, BV173 (Leukemia) [69] KCP-4 Cisplatin (Epidermoid carcinoma) [68]	ICC [66,67] ICP [68] IHC [69] Microarray [246] qPCR [66,68,69,246] WB [66–69]
ABCA7	Cisplatin [68] Daunorubicin [36]		Breast [109]	IHC [110,254]	CCRF/ADR5000, HL60/AR (Leukemia) [36]	CVA [68] FC [255]

	Doxorubicin [36] Paclitaxel [128]	Paclitaxel / FEC (Fluorouracil + Epirubicin + Cyclophosphamide) [109] Paclitaxel + Cisplatin / Carboplatin [110]	Ovarian [110,254] Pancreas [197]	qPCR [109,110,197,254] WB [109]	HNO97, PCTX+5-FU+CDDP-R (Head and neck squamous cell carcinoma) [128] KCP-4 Cisplatin (Epidermoid carcinoma) [68] SKOV-3, ABCA7 (Ovarian) [254] Y79 (Retinoblastoma) [255]	ICP [68] IHC [254] Microarray [36,128] qPCR [36,68,128,254,255] WB [68,254]
ABCB1	Actinomycin-D [107,256] Afatinib [257] Arsenic trioxide [258,259] Bortezomib [260] Carfilzomib [260–262] Ceritinib [263] Cisplatin [259,264–269] Cytarabine [259]	CMF (Cyclophosphamide + Methotrexate + Fluorouracil) [113,217] Consolidation: 6-Mercaptopurine + Cytarabine + Cyclophosphamide Docetaxel / CAX (Cyclophosphamide + Doxorubicin + Capecitabine) [137]	Acute lymphoblastic leukemia [248] Breast [113,137,217,268,290,300,301] Colorectal [302] Gastric [265,303]	FC [248] IHC [113,264,266,267,300,301,303,305–308] Immunocytofluorescence [266] Microarray [267,305]	A2780TR2, W1TR, SKOV-3TR2 (Ovarian) [298] A431/ABCB1 (Breast); MDCKII/ABCB1 (Canine kidney) [294] A549/DDP, A549/CHD1L, (Lung-NSCLC) [267] A549/DDP, A549/MALAT1 (Lung-NSCLC) [269] A549-R, H520-R (Lung-NSCLC) [260] AGS, MGC-803 (Gastric) [265]	ATPase [112,274,278,285] ChIP [284] Confocal microscopy [15,272,275] CVA [89,126,273,274,277,282,283,285,290–292,296,256,299,300,304,258,2

	Dasatinib [112,270] Daunorubicin [15,259,271] Docetaxel [87,272,273] Doxorubicin [15,36,88,89,107,108,126,260,273–280] Epirubicin [15,280] Eribulin [276] Erlotinib [16,281,282] Etoposide [88,89,107,108,259,273,279,280,283] Fluorouracil [284,285] Gefitinib [286]	FAC (Fluorouracil + Doxorubicin + Cyclophosphamide) [113,137,217,300] FEC (Fluorouracil + Epirubicin + Cyclophosphamide) [113,217,300] <u>Induction:</u> Vincristine + Doxorubicin + Asparaginase + Prednisone [248] Protocol M: Methotrexate [248] Taxane [113] / Fluorouracil [113]	Hepatocellular carcinoma [136] Non-small cell lung cancer [267,304] Oral squamous cell carcinoma [266] Osteosarcoma [264,305] Ovarian [290] Pancreas [306] Sarcoma [307] Urothelial [308]	PCR [136,300,308] qPCR [137,217,248,268,290,303,304] RNA-seq [290] WB [265,302]	AOCS18.5, AOCS21.2 [290] AsPC-1, PANC-1-EGFP (Pancreas) [306] BEL/5-FU-R (Hepatocellular carcinoma) [126] Caco-2 (Colorectal) e MDCKII/Pgp 1 (Canine Kidney) [288] CCRF/ADR5000 – (Leukemia) [36] CEM/VLB-R (Leukemia) [261] FaDu/CDDP-R (Hypopharyngeal) [266] GI-112 (Colorectal) [309] H23/Carf-R (Lung-NCSLC), DLD-1/Carf-R (Colorectal) [262] H69/VP (Lung-SCLC) [108] HCC1937, HCC1937-R (Hepatocellular carcinoma), MCF-10A (Breast) [296]	64,266,267,269–271, 294] ELISA[285] FC [89,107,112,126,260,261,266–273,275,279,286,287,294,302,304,306] FISH [112,283] Fluorescence microscopy [274,278] HPLC [88,89,282,288,297] HPLC-MS [112,272,289] HPLC-MS/MS [294] ICC [290]

	Idarubicin [287] Imatinib [111] Irinotecan [89,108] Irinotecan [288] Lapatinib [289] Liposomal doxorubicin [290] Mitoxantrone [15,16,88,278] Osimertinib [291] Paclitaxel [15,133,260,262,274,276,278,290,292,293] Ribociclib [294,295] Talazoparib [296] Temozolomide [297] Teniposide [108]				HCT116 /DOX-R, LoVo/DOX-R (Colorectal) [302] HepG2/AS (Hepatocellular carcinoma), SGC7901/AS (Gastric) [258] HeyA8MDR (Ovarian) [293] HL-60/5-FU-R (Leukemia) [285] HL-60/RS (Leukemia) [259] HL60-ABCB1 [286] HOS, U-2OS (Osteosarcoma) [264] HOS-EC50.SR (Osteosarcoma) [107] K562/DXR, K562/VCR (Leukemia), L-MDR1 (Porcine kidney) [279] K562-ABCB1 (Leukemia) [112,270] KB/V1, Caco-2 (Colorectal) [87]	IF [107,256,272,273,296] IHC [15,269,280] Immunocytofluorescence [266] LC/MS [256] LC-MS/MS [16,111,257,263,281,291,295,299] LC-UV [16] Luciferase repórter [304] Microarray [36,107,133,276] Northern blot [15,89,108,279,283]

	Topotecan [15,89,298] Vemurafenib [299] Vinblastine [15,87,133,271,279,280] Vincristine [88,107,108,259,279,280] Vindesine [108] Vinorelbine [273,279]				KB-8-5 (Epidermoid carcinoma), Caco2/imatinib (Colorectal) [111] KB-C2 (Epidermoid carcinoma), HEK293-ABCB1 (Embryonic human kidney), K562/AO2 (Leukemia) [292] KB-C2 (Epidermoid carcinoma), SW620-Ad300 (Colorectal), HEK293-ABCB1 (Embryonic human kidney) [274] KK47/ADM (Urothelial) [280] LLCPK-MDR1 (Canine kidney) [282] L-MDR1 (Porcine kidney) [281] L-Mdr1a (Porcine kidney) [16,297] MCF7/Adria (Breast), KG1a (Leukemia) [89]	PCR [15,287,306,309] qPCR [36,107,111,126,133,258–260,262,264,267,268,272,276,277,283–285,290,293,294,296,298,301,304] Radioactivity [87,280] RNA-seq [272] WB [15,87–89,107,108,111,112,126,258–260,262,264,265,267–278,284,286,28

					MCF-7/DDP-R, MDA-MB-231/DDP-R (Breast) [268] MCF7/E, MDA-MB-231/E (Breast) [276] MCF7/TR (Breast), MESSA/Dx5, KHOS R2, U-2OS/DR (Sarcoma), OVCAR8/TR, SKOV3/TR (Ovarian) [278] MCF7-ADM (Breast) [301] MDCKII-ABCB1 (Canine kidney) [256,257,263,282,289,295,299] MDCKII-ABCB1 (Canine kidney) [291] MESSA-Dx5 (Sarcoma), K562-R7 (Acute myeloid leukemia) [287] NCI/ADR-RES, [133]	8,290,292,293,296,301,302,304] Whole Transcriptome TempO-Seq [260]

					NIH-3T3-MDR1-G185 (Mouse embryonic fibroblast) [271] PC9/GR (Lung-NSCLC) [304] R-HepG2 (Hepatocellular carcinoma) [275] RKO/5-FU-R, HCT116/5-FU-R (Colorectal) [284] RPMI 8226/Dox (Multiple myeloma) [88] S1-M1-80 (Colorectal), MCF-7 AdVp3000 (Breast) [15] SK-3/VP16-R, (Ovarian) [283] SKOV-3TR2, W1TR, A2780TR2 (Ovarian) [298] SUM159, MDA-MB-231/DR-TAX (Breast) [272] U-2OS/DX580; Saos-2/DX580 (Osteosarcoma) [273]	

ABCB2 / TAP1	Cisplatin [128] Daunorubicin [36] Fluorouracil [128] Gemcitabine [310] Paclitaxel [128]	Induction: Vincristine, Cytarabine, Daunorubicin, Etoposide [60] Paclitaxel / FEC (Fluorouracil + Epirubicin + Cyclophosphamide) [109] Paclitaxel + Cisplatin/ Carboplatin [110]	Acute myeloid leukemia [60] Breast [109] Ovarian [110] Pancreas [197]	IHC [110] Microarray [60] qPCR [60,109,110, 197] WB [109]	FG, PANC-1 (Pancreas) [310] HL60/AR (Leukemia) [36] HNO97, PCTX+5-FU+CDDP-R (Head and neck squamous cell carcinoma) [128]	FC [310] Microarray [128] qPCR [128,310] WB [310]
ABCB4 / MDR3	Daunorubicin [91] Doxorubicin [36,311,312] Paclitaxel [91] Vimblastine [91]		Pancreas [197] Sarcoma [307]	IHC [307] qPCR [197]	CCRF-ADR5000 (Leukemia) [36] LLC-PK1-MDR3 (Kidney) [91] MCF7-Dox (Breast) [311] MDCKII-ABCB4, MCF-7/DOX, MDA-MB-231/DOX (Breast) [312]	ChIP [312] FC [312] Microarray [36,311] PCR [91] qPCR [36,312] WB [91,312]

ABCB5	Carboplatin [313] Doxorubicin [314] Etoposide [313] Fluorouracil [133] Irinotecan [133]	FOLFIRI (Fluorouracil + Irinotecan + Leucovorin) / FOLFOX (Fluorouracil, Oxaliplatin, Leucovorin) [315]	Colorectal cancer [315] Melanoma [314,316] Merkel cell carcinoma [313]	IHC [313,314,316] qPCR [313,315]	G3361 (Melanoma) [314] MKL-1/ETP+CBP-R, WaGa/ETP+CBP-R (Merkel cell carcinoma) [313] SK-MEL-28 (Melanoma) [133] SW620, COLO741 (Colorectal) [315]	CVA [313,314] FC [313–315] IF [313,314] Microarray [133] qPCR [133,313–315] Transwell [315] WB [315]
ABCB6	Cisplatin [317] Daunorubicin [36] Doxorubicin [36] Fluorouracil [318] Irinotecan [283,318] Mitoxantrone [36] Vincristine [318]	FEC (Fluorouracil + Epirubicin + Cyclophosphamide) / Paclitaxel + Trastuzumab[57] Fluorouracil + Oxaliplatin[167]	[317] Breast [57] Colorectal [167] Glioma [319] Hepatocellular carcinoma [136,320] Non-small cell lung cancer Prostate [138]	IHC [317] Microarray [57] PCR [136,320] qPCR [138,167,319] Spectrofluorometric [319]	A549/CPT-R (Lung- NSCLC) [283] Huh7, HepG2, Hep3B (Hepatocellular carcinoma) [320] KAS, KB-B6N8, KM12C/5-FU-R [318] MCF7/CH1000 (Breast) [36] Mel Juso (Melanoma) [43] U87-ABCB6, T98-ABCB6 (Brain) [319]	CVA [318,319] FC [317,319] FISH [283] Microarray [36] Northen blot [283] qPCR [36,43,283,318–321] WB [318–320]

ABCC1	6-Mercaptopurine [322] Actinomycin-D [256] Arsenic trioxide [258,259] Carboplatin [323] Chlorambucil [324–327] Cisplatin [259,269,322,325, 328] Cladribine [17] Cyclophosphamide [329] Cytarabine [259] Daunorubicin [17,36,259,330–334] Docetaxel [137,273,335]	ABVD (Doxorubicin + Bleomycin + Vinblastine + Dacarbazine / MOPP (Mechlorethamine + Vincristine + Prednisone + Procarbazine-ABVD / CVPP (Cyclophosphamide + Vinblastine + Procarbazine + Prednisone-ABDIC (Doxorubicin + Bleomycin + Dacarbazine) / NOVP (Mitoxantrone + Vincristine +	Acute lymphoblastic leukemia [17,248] Breast [109,113,137,353,357] Colorectal cancer [139,167,343,358] Glioma [135] Hepatocellular carcinoma [136] Hodgkin´s Lymphoma [352] Non-small cell lung cancer [356]	Confocal microscopy [357] FC [248] IHC [113,135,352–354,357–359] Microarray[352,357] PCR [17,136,356] qPCR [109,135,137,139,167,197,248,343, 354,355,358] RNA-seq[135]	2008/MRP1 (Ovarian) [351] 2008/MRP1, 2008wt (Ovarian) [334] A549 (Lung-NSCLC) [328] A549/Dox, H1793/Dox (Lung-NSCLC) [336] A549/MALAT1, A549/DDP (Lung-NSCLC) [269] BEL/5-FU-R (Hepatocellular carcinoma) [126] Capan-1/MUC1, BxPC3 MUC1 (Pancreas) [339] COR-L23/R, MOR/R0.4 (Lung-SCLC) [329] GLC4/Ad (Lung-SCLC), S1-ABCC1 (Lung-NSCLC) [330] GLC4/ADR (Lung-SCLC), CHO-Chlr (Hamster Ovary), HeLa T5 (Cervix), HL60/ADR (Leukemia) [324]	ATPase [285] ChIP [284,336,339] Co-IP [335] Confocal microscopy [275,335,337] CVA [17,126,326,327,330,331,333,337,339,347,139,256,267,271,274,282,283,323,294] Dual-luciferase reporter [135] ELISA [285] FC [126,255,269,273,275,286,337,342]

	Doxorubicin [17,126,273,275,328,331–334,336–338] Epirubicin [325,332] Etoposide [259,273,283,325,328,332,333,338–342] Fluorouracil [284,285,343] Flutamide [344] Gefitinib [286] Gemcitabine [339,345] Ifosfamide [329] Melphalan [324,340] Methotrexate [334,346,347]	Vinblastine + Prednisone) [352] AC-T (Doxorubicin + Cyclophosphamide / Taxane) [113] CMF (Cyclophaphamide + Methotrexate + Fluorouracil) [353] CMF (Cyclophosphamide + Methotrexate + Fluorouracil) / Taxane [113] Consolidation: 6-Mercaptopurine + Cyclophosphamide + Cytarabine + Protocol M: Methotrexate [248] Docetaxel [137]	Ovarian [355] Pancreas [197] Sarcoma [354] Thyroid [359]	WB [109,358]	H69/AR (Lung-SCLC), HeLa T14 (Cervix) [350] H69/AR (Lung-SCLC), HeLa T5 (Cervix) [338] H69/AR (Lung-SCLC), KB-CV60 (Epidermoid carcinoma)[337] H69/E8 (Lung-SCLC), H82/E8 (Lung-SCLC) [325] HCC1937, HCC1937-R (Hepatocellular carcinoma), MCF-10A (Breast) [296] HCT116/OXA, HT29/OXA (Colorectal) [139] HeLa-T5, HeLa-T14 (Cervix) [332] HepG2/AS (Hepatocellular carcinoma) [258] HL-60/5-FU-R (Leukemia) [285] HL60/AR (Leukemia) [36]	Fluorescence spectroscopy [334] HPLC [17,327,334,335,341,347] ICC [347,357] IF [256,273,283,296,322,336,337] IHC [269,357] LC/MS [256] LC-ESI-MS/MS [357] Luciferase reporter [139,343] Microarray [36] MS (MALDI-TOF/TOF) [335]

	Mitoxantrone [17,348] Oxaliplatin [322,343] Sorafenib [349] Talazoparib [296] Temozolomide [135] Teniposide [17,333] Thiotepa [17] Topotecan [322] Vinblastine [325,350] Vincristine [17,259,328,330,332,333,337,338,350,351] Vinorelbine [273]	Epirubicin + Ifosfamide [354] FAC (Fluorouracil + Doxorubicin + Cyclophosphamide) / CAX (Cyclophosphamide + Doxorubicin + Capecitabine) [137] FEC-T / FEC-VNR (Fluorouracil + Epirubicin + Cyclophosphamide) + Taxane / Vinorelbine [113] Fluorouracil [113] Fluorouracil +/ or Oxaliplatin [167] <u>Induction:</u> Vincristine + Doxorubicin +			HL-60/RS (Leukemia) [259] HL60-ABCC1 [286] HT-29/ETP-R (Colorectal) [283] IGROV-1/OHP, IGROV-1/MRP1 (Ovarian), U2-OS/MRP1 (Osteosarcoma) [322] KB/VP-4 (Epidermoid Carcinoma [341] KB4D-10/MRP1 (Cervix), PC-3-ADR (Prostate) [344] LN229, U87 (Brain) [135] MCF7/VPα-a (Breast) [327] MCF7/VP-R (Breast) [348] MCF7/VPα (Breast) [326] MCF7-ABCC1 (Breast), 4T1-ABCC1 (Murine breast), HLEC (Human lymphatic endothelial), HUVEC (Human	Northern blot [283,325,326,331,332,338,348] PCR [258,324,333,339] qPCR [36,126,135,139,255,259,284,285,296,322,323,336,342,343,349,357,360] Radioactivity [17,327,329,332,340,341,350] Southern blot [348] Transwell [349] WB [126,135,139,258,259,269,273,2

		Asparaginase + Prednisone [248] Paclitaxel / FEC (Fluorouracil + Epirubicin + Cyclophosphamide) [109] Paclitaxel + Cisplatin [355] TC (Docetaxel + Cyclophosphamide) [113] Vinorelbine + Cisplatin / Gemcitabine + Cisplatin[356]			umbilical vein endothelial) [357] MDA-MB-231/FSIP1, SKBR3 (Breast) [335] MDCKII-ABCC1 (Canine kidney) [256] Mononuclear cells (Acute lymphoblastic leukemia) [17] NIH3T3-MRP1 (Embryonic mouse fibroblast) [346] OVCAR-3/CBP+HA, SKOV-3/CBP+HA, OVCAR-5/CBP+HA (Ovarian) [323] PLC/PRF/5-SorR, HepG2/SorR, M Hepatocellular carcinoma 97L/SorR (Hepatocellular carcinoma) [349] R-HepG2 (Hepatocellular carcinoma) [275]	75,284,286,296,322,324,326,328,330–333,335–339,342,344–346,348,351,357]

					RKO/5-FU/R, HCT116/5-FU/R (Colorectal) [284] Saos-2/DX580, U-2OS/DX580 (Osteosarcoma) [273] SKOV3/VP16-R (Ovarian) [342] SR3A (Lung-SCLC) [331] SW480, HCT116 (Colorectal) [343] T24/Gem, J82/Gem (Urothelial) [345] W9.5 (Embrionyc stem) [333] Y79 (Retinoblastoma) [255]	
ABCC2	Actinomycin-D [256] Arsenic trioxide [258] Carboplatin [130,323]	CAX (Cyclophosphamide + Doxorubicin + Capecitabine) [137] Docetaxel [137] FAC (Fluorouracil + Doxorubicin +	Breast [137] Chronic myeloid leukemia [365] Colorectal [167]	IHC [367] PCR [136] qPCR [137,167,365,367]	2008/MPR2 (Ovarian) [347] A549/cisR (Lung-SCLC), H460/cisR (Lung-NSCLC), HEK293-ABCC2 (Human embryonic kidney) [362] BEL/5-FU-R (Hepatocellular carcinoma) [126]	Chromatin immunoprecipitation (ChIP) [362] CVA [126,258,349,363,365–367]

	Cisplatin [130,361–363] Docetaxel [127,364] Doxorubicin [126,130] Etoposide [127,361,364] Fluorouracil [128] Gefitinib [130] Imatinib [365] Irinotecan [130] Methotrexate [347] Oxaliplatin [366] Paclitaxel [127,128] Sorafenib [349,367] Vimblastine [127,364] Vinorelbine [368]	Cyclophosphamide) [137] Fluorouracil + / or Oxaliplatin [167]	Hepatocellular carcinoma [136,367]		Claudin-2KD/A549 (Lung-SCLC) [130] HEK293-ABCC2 (Human embryonic kidney) [361] HepG2/LV-ABCC2, HuH7/LV-ABCC2 (Hepatocellular carcinoma) [367] HNO206/PCTX+5-FU+CDDP-R, HNO97/PCTX+5-FU+CDDP-R, HNO237/PCTX+5-FU+CDDP-R (Head and neck squamous cell carcinoma) [128] HNSCC/CDDP-R (Head and neck squamous cell carcinoma) [363] K562/R (Chronic myeloid leukemia) [365] KB/CP20 (Cervix)[361]	FC [126,361–363,366] HPLC [347,368] ICC [323,347,363] ICP/MS [366] IF [256] LC/MS [256] Luciferase reporter [130,365,367] Microarray [128,363] qPCR [43,126,128,130,258,323,349,361–363,365–367] Radioactivity [127,364]

					MDCKII-ABCC2 (Canine kidney) [127,256,364,368] Mel Juso (Melanoma) [43] OV-90/CBP+HA, OVCAR-5/CBP+HA (Ovarian) [323] PANC-1 (Pancreas), Caco-2 (Colorectal) [366] PLC/PRF/5/Sor-R, HepG2/Sor-R, MHCC97L/Sor-R (Hepatocellular carcinoma) [349] SGC7901/AS (Gastric), HepG2/AS (Hepatocellular carcinoma) [258]	RNA immunoprecipitation [367] Transwell [349] WB [126,130,258,363–365,367]
ABCC3	Carboplatin [323] Cisplatin [128,328] Daunorubicin [36] Doxorubicin [36,328]	Paclitaxel + Cisplatin / Carboplatin [110]	Hepatocellular carcinoma [136] Ovarian [110] Pancreas [197]	FC [373] IHC [110] PCR [136] qPCR [110,197]	PLC/PRF/5/Sor-R, HepG2/Sor-R, MHCC97L/Sor-R (Hepatocellular carcinoma) [349] A549 (Lung-NSCLC) [328]	Confocal microscopy [369] CVA [328,349,372] FC [372,375]

	Etoposide [328,369–371] Methotrexate [346,370–372] Mitoxantrone [36] Paclitaxel [128] Sorafenib [349] Teniposide [369,370] Vincristine [328,371]			RNA-seq [374]	HNO97/PCTX+5-FU+CDDP-R (Head and neck squamous cell carcinoma) [128] OVCAR-3/CBP+HA, SKOV-3/CBP+HA, OV-90/CBP+HA, OVCAR-5/CBP+HA (Ovarian) [323] AsPC1/ABCC3, HPAFII/ABCC3, CFPAC-1/ABCC3 (Pancreas) [375] MDA-MB-231/MTX-R (Breast) [372] MCF7/CH1000 (Breast) [36] MRP3-38, MRP3-77 (Kidney) [369] 2008/MRP3-8, MDCKII/MRP3-17 (Canine Kidney) (Ovarian) [370] HEK/MRP3-5 (Embryonic kidney) [346]	HPLC [369,370] ICC [370] IF[370] IHC [369,375] Microarray [36,128] qPCR [36,128,323,349,372] Radioactivity [369] Transwell [349] WB [328,346,369–372,375]

					HEK/MRP3-5 (Embryonic kidney) [371]	
ABCC4	6-Mercaptopurine [322] Carboplatin [140] Cisplatin [322] Cyclophosphamide [376,377] Cytarabine [378] Daunorubicin [36] Doxorubicin [379,380] Ifosfamide [376] Irinotecan [377] Oxaliplatin [322] Topotecan [322]	Paclitaxel / FEC (Fluorouracil + Epirubicin + Cyclophosphamide) [109]	Breast [109,379] Hepatocellular carcinoma [136] Ovarian [32] Pancreas [197,381]	IHC [379] PCR [136] qPCR [32,109,197,379] RNA-seq TCGA-PAAD [381] WB [109]	BxPC-3/MRP4, PANC-1 (Pancreas) [381] GSF-0686, MG63/DOX (Osteosarcoma) [380] HEK293/CP-R (Embryonic kidney) [376] HL60/AR (Leukemia) [36] IGROV-1/OHP, 2008/MRP4 (Ovarian) [322] MCF-7/ADR-R (Breast) [379] Mel Juso (Melanoma) [43] MRP4/HepG2 (Hepatoma) [376,377] OCI-AML3/ARA-C (Leukemia), Saos 2-ABCC4, OCI-AML3/ARA-C-R (Acute myeloid leukemia) [378] U2-OS/MRP4 (Osteosarcoma) [322]	CVA [140,376–378] FC [381] HPLC [377,378] ICP-OES [140] IF [322] LC-MS/MS [380] Luciferase reporter [140] Microarray [36] PCR [378,380] qPCR [36,43,140,255,322,376,379,381] Radioactivity [378] Transwell [379]

					Y79 (Retinoblastoma); Y79/CR (Retinoblastoma) [140]	WB [140,322,376,378–381]
ABCC5	6-Mercaptopurine [382] 6-Thioguanine [382,383] Cisplatin [384,385] Daunorubicin [36] Docetaxel [137,386] Doxorubicin [36,383,386] Fluorouracil [383,387] Methotrexate [134,383] Mitoxantrone [36] Oxaliplatin [383] Paclitaxel [128] Pemetrexed [383]	CAX (Cyclophosphamide + Doxorubicin + Capecitabine) [137] Docetaxel [137] FAC (Fluorouracil + Doxorubicin + Cyclophosphamide) [137] FEC (Fluorouracil + Epirubicin + Cyclophosphamide) / Paclitaxel + Trastuzumab [57] Paclitaxel / FEC (Fluorouracil + Epirubicin +	Hepatocellular carcinoma [136] Pancreas [197] Breast [57,109,137] Prostate [386]	IHC [386] Microarray [57] PCR [136] qPCR [109,137,197] WB [109,386]	Capan-1/5FU-R (Pancreas) [387] H1155/DDP-R (Lung-NSCLC), H1334/DDP-R (Lung-NSCLC) [384] HEK293/MRP5E, HEK293/MRP5I (Human embryonic kidney) [134] HEK293/MRP5E, HEK293/MRP5I (Human embryonic kidney), MDCKII/MRP5-14, MDCKII/MRP5-15 (Canine kidney) [382] HEK-MRP5 (Human embryonic kidney) [383] HNO206/PCTX+5-FU+CDDP-R,	Confocal microscopy [382] CVA [386,387] HPLC [134,382,383] ICC [382] Luciferase reporter [386] Microarray [36,128] qPCR [36,128,384,386,387] WB [134,382,383,387,388]

		Cyclophosphamide) [109]			HNO97/PCTX+5-FU+CDDP-R, HNO237/PCTX+5-FU+CDDP-R (Head and neck squamous cell carcinoma) [128] LNCaP, PC-3 (Prostate) [386] MCF7/CH1000 (Breast) [36]	
ABCC10	Cisplatin [389] Cytarabine [390] Docetaxel [390–396] Doxorubicin [391] Fluorouracil [128,397] Gefitinib [398] Gemcitabine [129] Lipo-Doxorubicin [389] Paclitaxel [128,129,292,390–396,399–401]	<u>Induction:</u> Vincristine, Cytarabine, Daunorubicin, Etoposide [60] Paclitaxel / FEC (Fluorouracil + Epirubicin + Cyclophosphamide) [109] Paclitaxel + Carboplatin / Anthracycline Gemcitabine [129]	Acute myeloid leukemia [60] Breast [109,129] Colorectal [397] Hepatocellular carcinoma [136] Ovarian [32] Pancreas [197] Prostate [138]	IHC [397] Microarray [60,129] PCR [136] qPCR [32,60,109,129,138,197,397] WB [109]	H292/GR (Lung-NSCLC), PC-9 /GR (Lung-NSCLC) [398] HEK/MPR7 (Embrionary kidney) [394–396,399,401] NCI-H23-TXR (Lung-NSCLC) [400] LLC-PK1-ABCC10 (Porcine kidney) [390] J7-shNEK2 (Hepatocellular carcinoma) [389] SKBR3, HS578T, MDAMB231, T47D, MCF7 (Breast) [129]	ATPase Assay [390] Confocal microscopy [390] CVA [292,391–396,398–401] CytoScan HD Array [129] DNA Sequencing [129] FC [394,396–398]

	Tamoxifen [390] Vinblastine [391–396] Vincristine [391,392,394–396,401] Vinorelbine [393–395]				HEK-MRP7-C17, HEK-MRP7-C18 (Embrionary kidney) [391] HNO206/PCTX+5-FU+CDDP-R, HNO97/PCTX+5-FU+CDDP-R (Head and neck squamous cell carcinoma) [128] HEK293-ABCC10 (Embryonic human kidney) [292] HEK/MPR7-2 (Embrionary kidney) [393,401] HT-29/5-FU, HCT-8/5-FU (Colorectal) [397]	IF [394,395] LC-MS/MS [398] Microarray [128,129] Micro-WB array [400] PCR [392,394] qPCR [128,389,397,398,400] Radioactivity [390–393,395,396,399,401] RNA-seq [398] WB [292,389–401]
ABCC11	Eribulin [276] Fluorouracil [132,276,402–404]	FEC (Fluorouracil + Epirubicin + Cyclophosphamide)	Breast [57,109,404,406,407]	IHC [406,407]	HeLa/ABCC11-538G [403] LLC-PK1/MRP8 (Kidney) [132]	CVA [402–405] HPLC-MS/MS [404]

	Methotrexate [402,403,405] Pemetrexed [405] Tamoxifen [404]	/ Paclitaxel + Trastuzumab [57] Paclitaxel / FEC (Fluorouracil + Epirubicin + Cyclophosphamide) [109]	Hepatocellular carcinoma [136] Non-small cell lung cancer [403]	Microarray [57,406] PCR [136] qPCR [109,404,407] WB [109]	MCF7 (Breast) [404,407]MCF7/E, MDA-MB-231/E (Breast) [276] PC-6/FU23-26 (Lung-SCLC) [402] PC-6/MTA-R (Lung-SCLC) [405]	Microarray [276] qPCR [276,402–405,407] WB [132,276,403–405,407]
ABCE1	Doxorubicin [163] Fluorouracil [171] Temozolomide [164]	Doxorubicin [163] Fluorouracil / Oxaliplatin [167] Paclitaxel / FEC (Fluorouracil + Epirubicin + Cyclophosphamide) [109]	Breast [109,162] Colorectal [167] Glioma [164] Hepatocellular carcinoma [136] Ovarian [32] Small-cell lung cancer) [163]	IHC [162] PCR [136] qPCR [32,109,163,164,167] WB [109,163,164]	95-D (Lung) [408] A549 (Lung-NSCLC) [171] A549 (Lung-NSCLC) [42] H69/ADR-R (Lung-SCLC) [163] LTEP-a-2/ABCE1 (Lung-NSCLC) [42,165,166,409] MCF-7 (Breast) [162] Mel Juso (Melanoma) [43] U87, A172 (Glioma) [164] Y79 (Retinoblastoma) [255]	Co-IP [166] CVA [42,162,163,171,408,409] FC [162–165,255,409] IF [162,165,166,409] Luciferase repórter [163] Microarray [42] MS/ MS [166]

						PCR [42,171,408] qPCR [43,163–165,255,409] Transwell [162,166,409] WB [42,162–166,408,409]
ABCF2	Cisplatin [180] Doxorubicin [36,277] Oxaliplatin [183]	Paclitaxel / FEC (Fluorouracil + Epirubicin + Cyclophosphamide) [109] Platinum-based chemotherapy [179]	Breast [109] Ovarian [32,178–180]	IHC [178,180] Microarray [179] qPCR [32,109,179] WB [109,179]	293T-ABCF2 (Human embryonic kidney) [179] A2780/cp (Ovarian) [180] BGC823/L-OHP (Gastric) [183] CEM/ADR5000 (Leukemia) [36] Hep-G2/DOX (Hepatocellular carcinoma) [277] Mel Juso (Melanoma) [43] Y79 (Retinoblastoma)	ChIP [180] FC [180] FC [180,255] ICC [179] IF [179,180] Luciferase repórter [180] Microarray [36,180] qPCR [36,43,180,183, 255,277]

						WB [179,180,183]
ABCG1	Cisplatin [410,411] Daunorubicin [36] Doxorubicin [36,107] Etoposide [107] Mitoxantrone [36]	CAX (Cyclophosphamide + Doxorubicin + Capecitabine) [137] Docetaxel [137] FAC (Fluorouracil + Doxorubicin + Cyclophosphamide) [137] Paclitaxel / FEC (Fluorouracil + Epirubicin + Cyclophosphamide) [109]	Breast [109,137] Pancreas [197] Prostate [61]	qPCR [61,109,137,197] WB [109]	H1299, A549, A549/DDP (Lung-NSCLC) [411] HOS-EC50.SR (Osteosarcoma) [107] K1861/ABCG1 (Glioma) [412] MB49/ABCG1 (Urothelial), B16-F1/ABCG1 (Melanoma) [196] MCF7/CH1000 (Breast) [36] SKOV-3, OVCA-429, OVCA-420, A2780cis (Ovarian) [410]	Bioluminescense imaging [196,412] ChiP [411] CVA [410,411] FC [107,196] IF [107] IHC [412] Luciferase repórter [411] Microarray [36,107] qPCR [36,107,196,411] WB [107,410–412]
ABCG2	Afatinib [257]	CAX (Cyclophosphamide	Breast [137,215–221]	CVA [225]	4B.65, K114 (Mice Eca109/ABCG2 [420]	ATPase [112,285]

	Arsenic trioxide [259] Bleomycin [413] Ceritinib [263] Cisplatin [224,225,259,363, 410,414] Cytarabine [259,413] Dasatinib [112,270] Daunorubicin [15,36,259,415] Docetaxel [414] Doxorubicin [15,36,210,277,41 3,415–420] Epirubicin [15] Erlotinib [16,281,282]	+ Doxorubicin + Capecitabine) [137] CMF (Cyclophosphamide + Methotrexate + Fluorouracil) [217,220] Docetaxel [137] Epirubicin+ Cyclophosphamide + 5-fluorouracil / Docetaxel / Trastuzumab [218] FAC (Fluorouracil + Doxorubicin + Cyclophosphamide) [137,217,220] FEC (Fluorouracil + Epirubicin + Cyclophosphamide) [217,220]	Colorectal [222–225] Esophageal [420] Hepatocellular carcinoma [426] Nasopharyngeal carcinoma [414] Pancreas [197,226] Small-cell lung cancer [227] Thyroid [359]	FC [218,221,414] FISH [221] ICC [414] IF [221,414] IHC [215,216,222,226,227,359,420,426] Microarray [215] PCR [221,223,420] qPCR [137,197,217–219,224,225,414,420]	Eca109/ADM (Esophageal) [419] HCC1937, HCC1937-R (Hepatocellular carcinoma), MCF-10A (Breast) [296] HCT116/5-FU-R, RKO/5-FU-R (Colorectal) [284] HCT116-SN50 (Colorectal) [223] HeLa/SN-38 (Cervical) [413] Hep-G2/DOX (Hepatocellular carcinoma) [277] HL-60/5-FU-R (Leukemia) [285] HL60/PLB-ABCG2 [286] HL-60/RS (Leukemia) [259] HNSCC/CDDP-R (Head and neck squamous cell carcinoma) [363]	ChIP [284,417] Confocal microscopy [15,417,425] CVA [282,283,296,361,410,417,418,420,425,427, 294] ELISA [285] FC[112,222,223,270,286,363,415,416,419,420,422,425] FISH [112] HPLC [282,297,416,423] HPLC-MS [112] ICC [363] IF [296,413,425]

	Etoposide [259,413,416,421] Fluorouracil [224,284,285,413, 414,416,418] Gefitinib [286] Imatinib [111,422] Irinotecan [223,413,423] Lapatinib [289] Methotorexate [413,416,424,425] Mitoxantrone [15,16,36,210,223, 413,415,416,423–425] Nilotinib [112,422] Osimertinib [291] Oxaliplatin [224,418]	FEC (Fluorouracil + Epirubicin + Cyclophosphamide) / Tamoxifen [219] Platinum-based combination chemotherapy [227] Taxane /Anthracycline [220] TEC (Docetaxel + Epirubicin + Cyclophosphamide) [221]		Transcriptomic [220] WB [225,414]	IGROV-1/T8 (Ovarian), MDCKII-ABCG2 (Canine kidney) [282] K562-ABCG2 (Leukemia) [112,422] K562-Dox (Leukemia) [270] kidney) [421] kidney), MDCKII-ABCG2 (Canine MCF7, BT20 (Breast), Igrov/T8(p75)-40 (Ovarian) [219] MCF-7/ADR (Breast) [417] MCF-7/BCRP (Breast) [416] MCF7/CH1000 (Breast) [36] MCF-7/MR (Breast) [425] MCF7/MR (Breast), Caco2/imatinib (Colorectal) [111] MCF-7/MX (Breast) [424]	IHC [15,425] LC-MS/MS [16,85,111,257, 263,281,291,299] LC-UV [16] Microarray [36,363] Northern blot [15,210,219,415 ,421,423] PCR [210,223,413,415,418,419,421,423] qPCR [15,36,111,219, 220,259,277,284,285,296,298,363,417,424,427]

	Paclitaxel [224,414] Regorafenib [85] Talazoparib [296] Temozolomide [297] Teniposide [421] Topotecan [15,210,298,413,423,425] Vemurafenib [299] Vincristine [259]				MCF-7-AdrVp, MCF-7-ABCG2 (Breast) [415] MCF7-AdVp3000 (Breast), S1-M1-80 (Colorectal) [15] MDA-MB-231, BT549 (Breast) [220] MDA-MB-231/DOX (Breast) [427] MDCKII/ABCG2 (Canine kidney) [291] MDCKII-ABCG2 [85,257,263,289,299] MDCKII-Bcrp1 (Canine kidney) [16,297] OXA-R LoVo (Colorectal) [418] Saos2-BCRP (Osteosarcoma) [281] SKOV-3, OVCA-429, OVCA-420, A2780cis (Ovarian) [410]	Radioactivity [421,422] Southern blot [421,424] Transcriptome [220] WB [15,111,112,219,223,259,270,284,286,296,363,410,413,417–419,424,425]

					SKOV-3TR1, SKOV-3TR2, W1TR, A2780TR1 (Ovarian) [298] SW480 (Colorectal) [222] T6400 (Mice Embryonic cell), M32 (Mice Embryonic cell), D320 (Mice ear cell) [210] T8 , MX3 (Ovarian) [423]	

Note: SCLC - Small cell lung cancer; NSCLC - Non-small cell lung cancer; ChIP - Chromatin immunoprecipitation; ChIP-seq - Chromatin Immunoprecipitation Sequencing; Co-IP - Co-Immunoprecipitation; CVA - Cell Viability Assay; ELISA - Enzyme-linked immunoassay; FC - Flow cytometry; FISH - Fluorescence In Situ Hybridization; HPLC - High-performance liquid chromatography; HPLC-MS - High-performance liquid chromatography/mass spectrometry; ICC - Immunocytochemisty of cultured cells; ICP - Inductively Coupled Plasma; ICP/MS - Inductively coupled plasma mass spectrometry; IF – Immunofluorescence; IHC – Immunohistochemistry; LC-MS/MS - Liquid chromatography tandem mass spectrometry; LC-UV - Liquid chromatography interfaced to ultraviolet detection; LSC - Liquid scintillation counting; Micro-WB array - Micro-Western Blot Array; MS/MS - Tandem mass spectrometry; PCR - Polymerase chain reaction; qPCR - Quantitative real-time Polymerase Chain Reaction; RIP - RNA immunoprecipitation; RNA-seq - RNA Sequencing; RT-PCR - Semiquantitative reverse-transcription polymerase chain reaction; WB - Western Blot.

4. The 20 human ABC proteins and their association with MDR in cancer

Considering our selection criteria, from the 48 human ABC proteins, 20 were listed to be associated with MDR in cancer (Table 1). The global analysis of the literature review included 255 studies (insert Fig. 2A). From these studies, 160 were exclusively *in vitro* studies and 46 exclusively clinical studies. In addition, 49 studies included both cell-based and clinical approaches. Among the 20 ABC proteins selected, P-gp (ABCB1), MRP1 (ABCC1) and ABCG2 were the most studied ABC transporters (Fig. 2A).

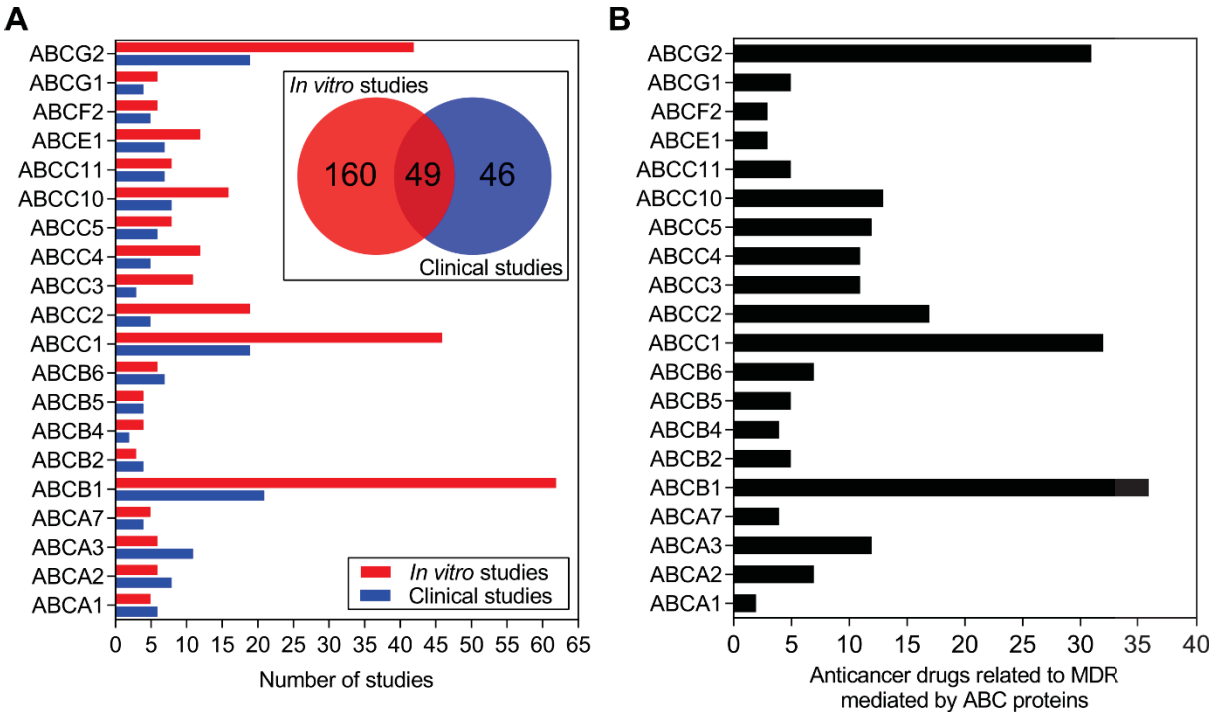

Figure 2: The 20 ABC proteins overexpressed and related with MDR in cancer. Numerical values of the studies presented in table 1 that meet all these three selection criteria for each ABC protein: (1) at least 2 studies containing a chemotherapeutic agent described as a substrate or associated with resistance; (2) at least 2 studies showing overexpression in cancer samples - clinical studies and (3) at least 2 studies showing overexpression in cancer cell lines - *in vitro* studies. (**A**) Number of studies. The insert corresponds to a Venn diagram showing the number of *in vitro* studies, clinical studies and studies that used both approaches. (**B**) Number of anticancer drugs related to MDR.

From the overall studies, a total of 55 different anticancer drugs were related with MDR mediated by ABC proteins. Among them, 53 were associated with the three most important ABC transporters: P-gp, MRP1 and ABCG2. Each one of these three ABC transporters were associate with more than 30 anticancer drugs (Fig. 2B). Other six ABC proteins (ABCA3, ABCC2-5 and ABCC10) were associated with more than 10 anticancer drugs each (Fig. 2B).

Sixteen anticancer drugs were related with five or more of these 20 ABC proteins, as following: doxorubicin (17 ABC proteins), cisplatin (15), daunorubicin (13), paclitaxel (11),

fluorouracil (11), mitoxantrone (9), etoposide (8), methotrexate (7), vincristine (6), cytarabine (6), irinotecan (6), docetaxel (6), oxaliplatin (6), vinblastine (6), gefitinib (5), carboplatin (5). In addition, an important overlap of the anticancer drugs was observed by P-gp, MRP1 and ABCG2.

Also based in the table 1, it was possible to verify that P-gp and MRP1 were related with a higher number of different neoplasia (Fig. 3A). In addition, considering exclusively the clinical studies, 9 (ABCA1-3, B1, B6, C1, C10, E1 and G2) from the 20 ABC proteins appear in five or more different neoplasia (Fig. 3A). Breast cancer was the most associated with the overexpression of ABC proteins, followed by pancreas, hepatocellular carcinoma, ovarian, colorectal and non-small cell lung cancer (Fig. 3B). It is important to note that lack of clinical studies in some neoplasia, such as epidermoid carcinoma, cervical and retinoblastoma, that until now were not associated with the presence of ABC proteins (Fig. 3B).

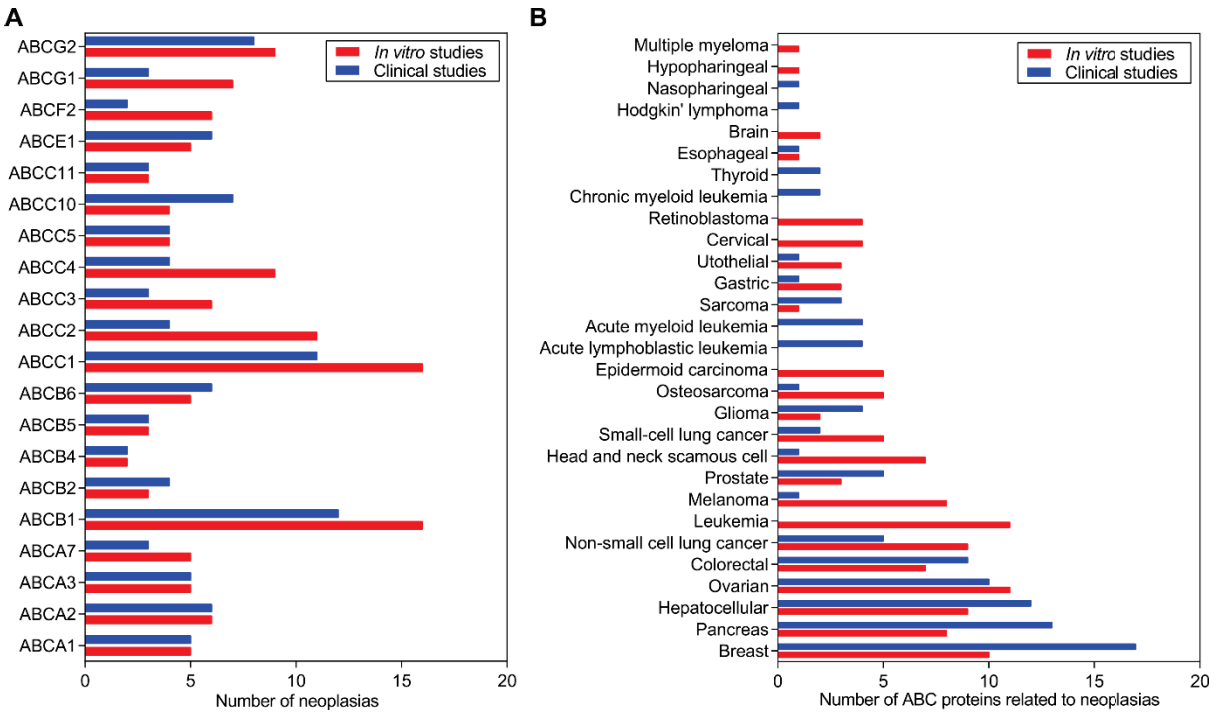

Figure 3: The 20 ABC proteins overexpressed and related with MDR in cancer. Numerical values of the studies presented in table 1 that meet all these three selection criteria for each ABC protein: (1) at least 2 studies containing a chemotherapeutic agent described as a substrate or associated with resistance; (2) at least 2 studies showing overexpression in cancer samples - clinical studies and (3) at least 2 studies showing overexpression in cancer cell lines - *in vitro* studies. (**A**) Number of neoplasias *versus* the 20 ABC proteins. (**B**) Number of ABC proteins *versus* each neoplasia. Leukemia, epidermoid carcinoma, cervical, retinoblastoma, brain, hypopharingeal and multiple myeloma appear only in studies *in vitro* due the specific cell lines used in the study. For the *in vitro* studies using leukemia and brain cells it was not possible to classify in subtypes.

5. Predicting clinical MDR mediated by ABC proteins

Cancer treatment success and curability rely on early diagnosis and a multimodal therapeutic approach. Depending on cancer type, status, morphological and molecular characteristics and patient conditions, cancer treatment can include surgical resection, chemotherapy and radiotherapy for, ideally, cure or durable remission [428]. Considering that the efficacy of chemotherapeutic regimens has been hampered by MDR mechanisms, mainly involving the overexpression of ABC transporters, it is very important to predict MDR in patients with cancer.

As shown in table 1, 53 anticancer drugs and 16 regimens were related to MDR mediated by the three most important ABC transporters (P-gp, MRP1 and ABCG2) due its overexpression in cancer cells. However, this association does not mean that all these drugs can be considered as substrates of ABC transporters. In this work, we considered as substrates of P-gp, MRP1 and ABCG2, only molecules that are transported outside of cells. We identified 34 anticancer drugs as substrates of these three ABC transporters (Fig. 4).

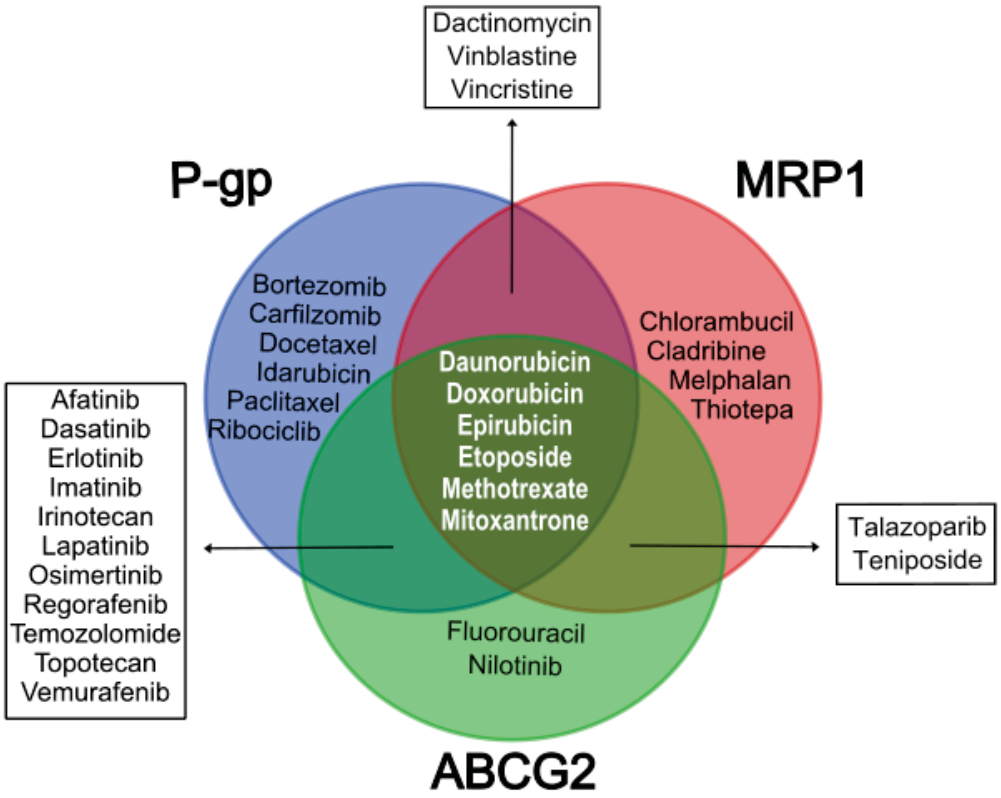

Figure 4: Venn diagram showing the 34 anticancer drugs that are substrates of one or more of the three most relevant ABC transporters: P-gp, MRP1 and ABCG2. These substrates were identified among the 55 drugs (monotherapy) associated with P-gp, MRP1 and ABCG2, according to the criteria for inclusion in table 1. To be considered as a substrate, the efflux mediated by P-gp, MRP1 and ABCG2 of these 34 drugs was confirmed by *in vitro* studies.

Considering P-gp, MRP1 and ABCG2, some anticancer drugs are exclusively transported by a unique of these ABC transporters, such as paclitaxel, that is transported only by P-gp (Fig. 4). However, most anticancer drugs are transported by two or three of these

ABC transporters. As shown in figure 4, it is observed an overlap of six anticancer drugs, including the anthracyclines daunorubicin, doxorubicin and epirubicin, the anthracycline derivative mitoxantrone, the antimetabolite methotrexate, and the topoisomerase inhibitor etoposide. It is important to note that these anthracyclines, due to their cytotoxic properties, are present in several protocols of treatment [429]. In contrast, the four substrates that are exclusively transported by MRP1 are not observed in the current protocols.

Interestingly, an overlap of 11 anticancer drugs are transported by both P-gp and ABCG2. The failure of most clinical trials using specific P-gp inhibitors [430] could be directly associated with this overlap, emerging the discussion about the use of specific or pan-inhibitors of these ABC transporters [8]. In addition, this number of substrates is probably underestimated, since some anticancer drugs were not included in the table 1 due the lack of studies, such as clofarabine, an effective antileukemic agent that is transported by ABCG2 [431].

To associate these 34 anticancer drugs with a specific cancer type, the clinical indication of each anticancer drug was obtained from Food and Drug Administration (FDA) (www.fda.gov/drugsatfda). Among the 20 different cancer types, breast cancer, lung cancer and acute lymphoblastic leukemia (ALL) showed the major number of anticancer drugs that are considered as substrate of at least one of these three main ABC transporters (Fig. 5).

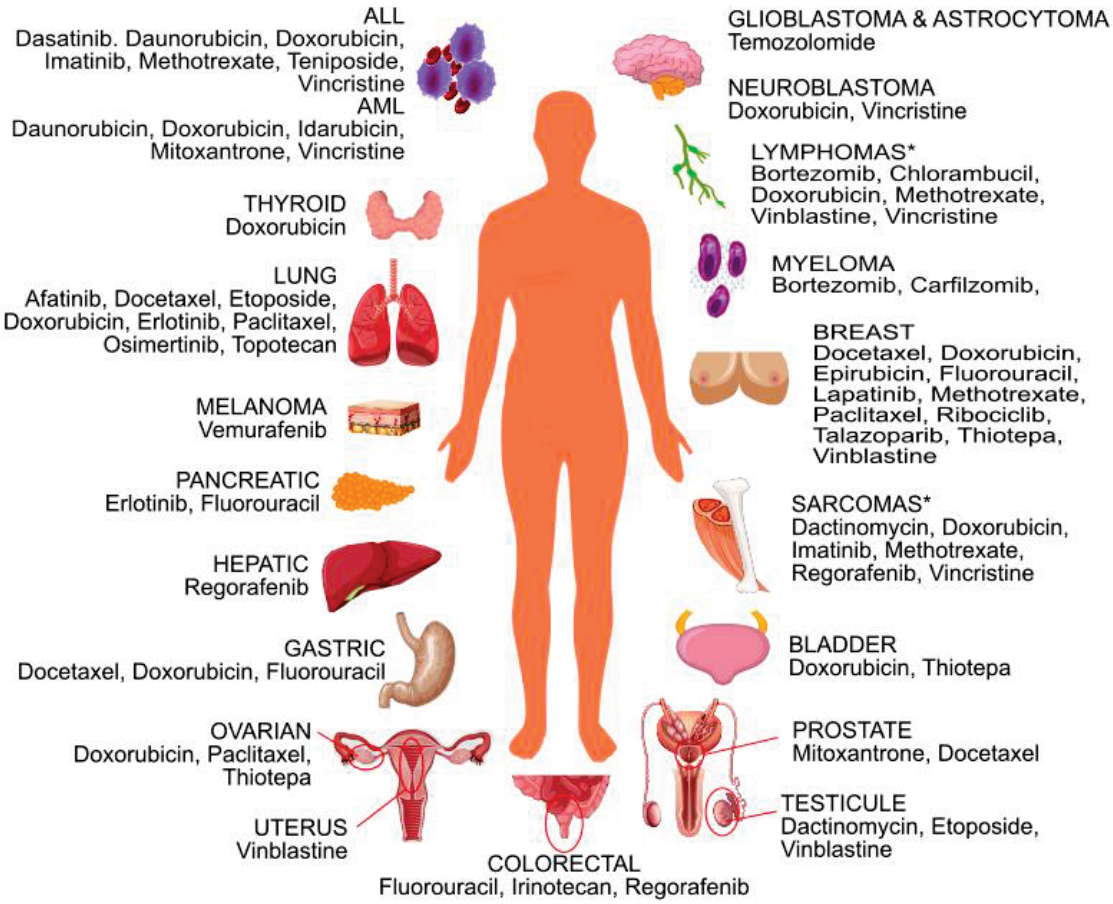

Figure 5: Targeted cancer type of the 34 anticancer drugs that are substrate of at least one of the three ABC transporters: P-gp, MRP1 and ABCG2. *Lymphomas and sarcomas are a heterogenous types of cancer. In lymphomas are included drugs to treat Hodgkin's, non-Hodgkin's, giant cell and mantle lymphomas. In sarcomas are included drugs to treat soft tissue sarcoma, osteosarcoma and gastrointestinal stromal tumor. To be associated with a specific tissue, it was only considered FDA-approved drugs, according to the clinical indication. To be considered as a substrate, the efflux mediated by P-gp, MRP1 and ABCG2 was validated by *in vitro* assays, as indicated in table 1.

This data suggest that the breast cancer is the most susceptible to the treatment failure due the MDR mediated by ABC transporters. Breast cancer is the most common cancer type, being fifth in mortality in terms of absolute numbers, showing a 5-year survival rate of 90%. However, for patients with metastatic breast cancer the 5-year survival rate decrease to 30% [1].

Based on histological molecular biomarkers, breast cancer can be classified as luminal A, luminal B/HER2-, luminal B/HER2+, HER2-enriched (non-luminal), and triple-negative (ER-, PR-, HER-), as reviewed by Harbeck and coworkers (2019) [432]. Based on the classification and stage, different strategies of treatment can be used, including neoadjuvant (preoperative), adjuvant, recurrent and metastatic. The most commonly used regimen include anthracyclines (doxorubicin and epirubicin), taxanes (docetaxel or paclitaxel), fluorouracil,

cyclophosphamide, methotrexate and carboplatin [433–435]. In addition, anthracyclines and taxanes are the most used anticancer drugs in mainly triple-negative breast cancer patients [436].

Treatment of breast cancer patients with standard AC (doxorubicin, cyclophosphamide) and CMF (cyclophosphamide, methotrexate and fluorouracil) regimens showed similar benefits, reducing the recurrence rates during the next 8 years by one-third and the mortality by 20 to 25%, when compared with patients that did not received chemotherapy [437]. Further, AC plus taxane regimens seems to be promising to improve the outcome, but additional studies are required [437].

There is a growing consensus in the literature that support the association of the overexpression of P-gp, MRP1 and ABCG2 with the acquired MDR phenotype in breast cancer patients [109,113,300,353,438]. For instance, Litviakov and colleagues (2013) observed a lower objective tumor response to the therapy in breast cancer patients that received neoadjuvant chemotherapy (NAC), including FAC (fluorouracil, doxorubicin and cyclophosphamide), CAX (cyclophosphamide, doxorubicin, and capecitabine) and docetaxel regimens [438]. In this study, the authors demonstrated a significant increase of mRNA levels of *ABCB1*, *C1*, *C2*, *C5*, *G1* and *G2* in non-responsive patients treated with FAC or CAX regimens. Additionally, the lower responsiveness to the docetaxel was associated with the overexpression of *ABCB1*, *C2*, *G1* and *G2* genes [438].

MDR mediated by ABC transporters was also demonstrated at protein levels by immunohistochemistry. Patients with locally advanced breast cancer treated with an anthracyclines-based regimen presented up-regulation of P-gp [300], and triple-negative breast cancer patients treated with an anthracycline/taxane-based regimen showed up-regulation of MRP1 levels [113].

For lung cancer, the 5-year relative survival rate is lower than 25%, reaching to 7% when the patient is diagnosed at advanced stage. Thus, lung cancer is considered the leading cause of cancer death [1]. Lung cancer is histologically divided in two main types: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), corresponding to 80-85% and 10-15% of the cases, respectively [439,440].

Successful treatment of cancer lung patients relies on early detection. NSCLC global 5-years survival rate is 18.6 to 29.8% [440]. Several biomarkers are described for NSCLC, however, additional studies are required for clinical validation [441,442]. Treatment protocols for NSCLC generally are based on platinum derivatives (carboplatin and cisplatin) in combination with other class of anticancer drug, including: docetaxel, paclitaxel, etoposide, mitomycin, ifosfamide, vinorelbine and cyclophosphamide [443]. For advanced stages, the combination with doxorubicin is described [170]. Targeted therapy is indicated by ESMO (2017) [444] and Ettinger and collaborators (2022) [445] to enhance responsiveness, which

includes afatinib, gefitinib, dacomitinib, erlotinib, osimertinib, vemurafenib, alectinib and atezolizumab [446]. Despite of these options and combinations, NSCLC is intrinsically resistant and are commonly not responsive to chemotherapy, which leads to poor patient prognosis and survival [447].

There are still a lack of molecular biomarkers in SCLC [448], that associated with MDR might reflect its high mortality, since the 5-years relative survival rate is 7% [449]. First-line treatment for SCLC consists of a combination of cisplatin/carboplatin plus etoposide. As soon resistance or relapse is detected, atezolizumab, durvalumab, irinotecan, paclitaxel, docetaxel, cyclophosphamide and gemcitabine might be used [450,451]. In addition, topotecan has been considered as a promising drug [452,453].

Considering both types of lung cancer, platinum drugs are widely used, and their association with MDR is well-known [454]. According to the literature revised here, platinum drugs are not substrates of P-gp, MRP1 and ABCG2 (Fig. 4). However, cisplatin is described as substrate of other ABC transporters, such as ABCC2 (MRP2) and ABCC3 [455,456]. Furthermore, immunohistochemical analysis revealed that the presence of P-gp and MRP2 are associated to a lower response to platinum-based chemotherapy in SCLC patients [457] and ABCG2 to a shorter survival in NSCLC patients [458]. In addition, overexpression of *ABCC1* was also associated to poor response to cisplatin and survival in advanced NSCLC patients [459]. Etoposide, that appears in some regimens of unresectable locally advanced NSCLC [444] is substrate of the three main ABC transporters (Fig. 4). Triller and colleagues (2006) demonstrated that the overexpression of MRP1 and P-gp after cisplatin/etoposide chemotherapy in SCLC patients was predictive to relapsed disease [460].

Although the large number of studies in solid tumors demonstrating the MDR mediated by ABC transporters, hematopoietic cancers are also susceptible to them. ALL is the most common type of cancer at young ages [461], but also affects adults, with a worse prognosis [462]. There are 16 molecular subtypes of ALL, as presented by Roberts (2018) and its classification is important to the management of the patients [463]. A known biomarker is BCR-ABL1 (Philadelphia chromosome), present in 3% of pediatrics and 25% of adults patients [464,465]. The survival rate is age-related [466]. The 5-years overall survival in the younger population is 90%, but in adults this rate decrease to 28-41% [440]. Jaramillo et al. (2019) and Rahgozar et al. (2014) discussed the impact of different ABC transporters in ALL disclosure, associating the lower drug-induced cell death of leukemic cells due to the efflux with an increased chance of relapse, which is the main cause of death in ALL [461,462]. ALL, as well leukemias in general, has the most complex protocols for treatment, consisting in standard chemotherapy and targeted therapy, depending of immunophenotype and cytogenetics, with tyrosine kinase inhibitors and antibodies [469,470]. The therapy consists in the three phases: induction, consolidation and maintenance [471]. Hematopoietic stem-cell transplantation after

induction is recommend in adults, due to an expected poor response to the chemotherapy and increased risk of relapse [468,472]. Standard regimens at induction phase depend of age and risk of relapse [473]. All regimens used in the induction phase are based in CALGB [474], COG [475], and hyper-CVAD regimens [476]. All these regimens contain the anticancer drugs vincristine and daunorubicin, that are transported by at least two of the main ABC transporters (Fig. 4). Together with these regimens, central nervous system prophylaxis is done with methotrexate and cytarabine with the highest dose to guarantee myeloablation [475,477]. As showed in figure 4, methotrexate is a substrate of P-gp, MRP1 and ABCG2.

Depending on the target expressed, tyrosine kinase inhibitors can be used, such as nilotinib, dasatinib and imatinib, to reverse and maintain cytogenetics response [478]. All of them are substrates for ABC transporters, therefore, is expected that they are subjected to resistance through efflux.

Most of the studies addressing ABC transporters as MDR mediators in leukemias is for adult acute myeloid (AML) [479]. However, ALL has gaining recent attention and increased expression of ABC transporters could be associated with MDR. For instance, P-gp might mediates resistance to imatinib [480]; *ABCC1* and *G2* in patients following BFM95 regimen, which includes vincristine, anthracyclines, and methotrexate [479]; *ABCC1*, *A2* and *A3* following treatment with vincristine and doxorubicin [481]; and *C1*, *G2*, *C4* and *C5* was correlated with *ex vivo* resistance to mitoxantrone [467].

Together, the knowledge of anticancer drugs as substrate for the main ABC transporters involved in clinical MDR may help to plan a more efficient treatment strategy to increase patient survival.

6. Concluding remarks

This study reveals the 20 ABC proteins most clinically related to MDR in cancer, through mechanisms of efflux to extracellular environment and intracellular sequestration of anticancer drugs. This panel of 20 ABC proteins (ABCA1-3, 7, ABCB1, 2, 4-6, ABCC1-5, 10, 11, ABCE1, ABCF2, ABCG1, 2) can be used as a signature of MDR mediated by ABC proteins. In addition, these proteins might be targeted of pharmacological strategies to overcome MDR including the use of non-substrates drugs and the use of new therapies to inhibition of these pumps.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Author statement

G.V. and V.R.M. designed the study. A.V.L.M., B.E.R., D.E.L., L.O.P., I.W.D. wrote the parts of the manuscript. A.V.L.M. created table 1. L.O.P. revised table 1. I.W.D. was responsible for the topic 2. D.E.L. created figure 1. B.E.R. created figures 4 and 5. G.V. and V.R.M. reviewed and edited the manuscript. All authors reviewed the manuscript.

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