1521-009X/50/1/76–85$35.00
Drug Metabolism and Disposition

https://doi.org/10.1124/dmd.121.000419
Drug Metab Dispos 50:76–85, January 2022

Special Section on ADME Databases-Minireview

Feature, Function, and Information of Drug Transporter–Related Databases

Jiayi Yin, Fengcheng Li, Zhaorong Li, Lushan Yu, Feng Zhu*, and Su Zeng*

Institute of Drug Metabolism and Pharmaceutical Analysis, College of Pharmaceutical Sciences, Zhejiang University, Hangzhou 310058, China (J.Y., F.L., L.Y., F.Z., S.Z.); Alibaba-Zhejiang University Joint Research Center of Future Digital Healthcare, Hangzhou 330110, China (Z.L., F.Z.); Innovation Institute for Artificial Intelligence in Medicine of Zhejiang University, Hangzhou 310018, China (F.Z.); and Zhejiang Province Key Laboratory of Anti-Cancer Drug Research, Cancer Center of Zhejiang University, Hangzhou 310058, China (S.Z.)

Received February 10, 2021; accepted August 20, 2021

ABSTRACT

With the rapid progress in pharmaceutical experiments and clinical investigations, extensive knowledge of drug transporters (DTs) has accumulated, which is valuable data for the understanding of drug metabolism and disposition. However, such data are largely dispersed in the literature, which hampers its utility and significantly limits its possibility for comprehensive analysis. A variety of databases have, therefore, been constructed to provide DT-related data, and they were reviewed in this study. First, several knowledge bases providing data regarding clinically important drugs and their corresponding transporters were discussed, which constituted the most important resources of DT-centered data. Second, some databases describing the general transporters and their functional families were reviewed. Third, various databases offering transporter information as part of their entire data collection were described. Finally, customized database functions that are available to facilitate DT-related research were discussed. This review provided an overview of the whole collection of DT-related databases, which might facilitate research on precision medicine and rational drug use.

SIGNIFICANCE STATEMENT

A collection of well established databases related to drug transporters were comprehensively reviewed, which were organized according to their importance in drug absorption, distribution, metabolism, and excretion research. These databases could collectively contribute to the research on rational drug use.

Introduction

Drug efficacy and safety are largely determined by multiple processes (absorption, distribution, metabolism, and excretion) that regulate pharmacokinetics (Terada et al., 2015). A variety of endogenous molecules (mostly proteins) are determinants of these processes (Giacomini et al., 2010). Typical examples of these molecules include drug-metabolizing enzymes that transform parent drugs to metabolites of very different physicochemical and pharmacological properties (Yu and Zhong, 2016; Yu et al., 2017; Hitchings and Kelly, 2019), and drug transporters (DTs) that mediate the uptake of endo/exogenous substances into cells as well as their efflux (Rodieux et al., 2016; To et al., 2017; Shu et al., 2019). Among these molecules, DTs are capable of 1) determining the pharmacokinetic profile of drugs by regulating their absorption, distribution, and excretion or indirectly modifying their metabolism (DeGorter et al., 2012; Yang et al., 2019), 2) affecting drug pharmacodynamics by delivering them to proper target sites, controlling differential drug concentrations among tissues or altering their interactions with other molecules (Hu et al., 2015), 3) inducing drug toxicity through DT's vulnerability to drug-drug interaction (DDI) or leading to drug resistance by reducing its concentration in targeted cells (Zhang and Hagenbuch, 2019), and 4) facilitating target discovery and rational use of the drug by revealing the mechanism of DDI, identifying the potential

This work was funded by National Natural Science Foundation of China [81973394] and Natural Science Foundation of Zhejiang Province [LR21H300001] and supported by the Alibaba-Zhejiang University Joint Research Center of Future Digital Healthcare, Alibaba Cloud, and Information Technology Center of Zhejiang University.

No author has an actual or perceived conflict of interest with the contents of this article.

dx.doi.org/10.1124/dmd.121.000419.

ABBREVIATIONS: ABCMdb, ABC proteins mutation database; ADME, absorption, distribution, metabolism, and excretion; CFMD, CF mutation database; dbSNP, NCBI database of genetic variation; DDI, drug-drug interaction; DT, drug transporter; encoMPASS, encyclopedia of membrane proteins analyzed by structure and symmetry; FDA, The United States Food and Drug Administration; FINDbase, frequency of inherited disorders database; hOAT2, human organic anion transporter 2; hOCT1, human organic cation transporter 1; iMusta4SLC, integrated mutational and structural analysis for solute carrier transporters database; IUPHAR/BPS, IUPHAR/BPS guide to pharmacology database; metrabase, Metabolism and Transport Database; METscout, metabolites enzymes and transporters database; OMIM, online mendelian inheritance in man database; PDB, RCSB protein data bank; PharmGKB, pharmacogenomics knowledgebase; PPTdb, pathogenic protist transmembranome database; SLC, solute carrier; TCDB, transporter classification database; Transformer, metabolism of xenobiotics database; TransportDB, genomic comparisons of membrane transporter systems; TTD, therapeutic target database; UniProt, universal protein knowledgebase; UCSF-FDA, University of California San Francisco–Food and Drug Administration; VARIDT, variability of drug transporter database.

therapeutic target or improving the treatment of specific disease (Garibsingh and Schlessinger, 2019). Due to the essential role of DTs in drug efficacy and safety, it is necessary to acquire as much DT-centered knowledge as possible (Li et al., 2017; Zhu et al., 2019; Tang et al., 2020; Wang et al., 2021; Zhou et al., 2021).

With the advancement of experimental analysis (Li et al., 2018a) and clinical investigation (Stopfer et al., 2016), an extensive amount of DT knowledge has accumulated and mainly involves five types of DT-centered information: 1) expression, distribution, and function (Lin et al., 2015), 2) epigenetic modification (Hirota et al., 2017), 3) structural conformation and variation (Zheng et al., 2018), 4) exogenous regulation (Li et al., 2018a), and 5) genetic polymorphism (Peng et al., 2016). Particularly, the data regarding DT's expression, distribution and function demonstrate its disease-differential expression (Evers et al., 2018), organism-dependent abundance (Durmus et al., 2015), tissue-specific distribution (Nixon et al., 2016), transporting functional family (Shen et al., 2017), and so on; the data of epigenetic modification on DT describe the DNA/histone methylation and acetylation (Liu et al., 2016), noncoding RNA regulation (Yu et al., 2019), and so on; the data of DT's conformation and structural variations involve species-specific evolution (Dias and Sa-Correia, 2014), the structures of the entire transporter (Penmatsa et al., 2013) and functional conserved/substrate-binding domain (Xue et al., 2016), and so on; the data of DT's exogenous regulation discuss the clinical drug-drug interactions (Kosa et al., 2018), regulatory substrate, inhibitor and inducer (Muller et al., 2018), and so on; the data describing DT's genetic polymorphisms provide the cytogenetic locations (Lewis and Girisha, 2020), disease indication induced by hereditary factor (Karimian et al., 2020), genetic variant and frequency (Veldic et al., 2019), and so on. The above knowledge is valuable for understanding the drug ADME process (Nigam, 2015; Ye et al., 2019), which is thus essential for current research on drug metabolism (Li et al., 2020b; Wang et al., 2020a; He et al., 2021) and disposition (Bai et al., 2016; Kawahara et al., 2020).

However, such valuable knowledge is largely dispersed in the literature, which hampers its utility and significantly limits its possibility for comprehensive analysis (Li et al., 2018b; Yang et al., 2020b). Therefore, a variety of databases have been constructed to offer DT-related data (Wang et al., 2020c; Yin et al., 2020; Saier et al., 2021). Some of them offer explicit information on drugs together with their corresponding transporters, and give special emphasis on DT variability (Yin et al., 2020); some others describe general transporters together with their (phylogenetic) classifications, and specifically highlight the ones of human origin (Elbourne et al., 2017); the remaining databases aim to provide general data on various transporters as a part of their data collection (UniProt, 2021). These databases guarantee the accessibility to DT-related knowledge, which is anticipated to be the key data resource for current ADME studies.

Therefore, a comprehensive review of these popular databases was conducted. First, the databases providing the data of clinically important drugs together with their corresponding transporters were discussed, which constituted the most important resources for DT-centered data. Second, several databases describing the general protein transporters and their functional families were reviewed, which were crucial for any study requiring transporter (especially DT) classification. Finally, the databases offering general transporter information as a part of their data collection were described, which could be adopted as essential complements to other available databases. The overview of these various types of databases were shown in Table 1.

Databases Providing Drugs and Their Corresponding Transporters

As estimated, approximately 10% (~2,000) of all proteins in the human genome are functionally associated with the transporting of endo or exogenous molecules (Hediger et al., 2013). However, regarding the transporting of clinically important drugs, the total number of involved DTs is still under debate (Yin et al., 2020). The valuable data of DTs together with their transporting drugs have been described in a variety of databases (Fig. 1), and the characteristic groups of data covered by different databases were comprehensively reviewed and discussed in Table 2.

Pairing Data between Drug Transporter and Pharmaceutical Agent. Several databases are providing the pairing data between DTs and pharmaceutical agents. As the most widely used data resources of pharmaceutical agents, Therapeutic Target Database [https://idrblab.org/ttd/, (Wang et al., 2020d)], DrugBank [https://go.drugbank.com/, (Wishart et al., 2018)], ChEMBL [https://www.ebi.ac.uk/chembl/, (Mendez et al., 2019)], IUPHAR/BPS guide to pharmacology [https://www.guidetopharmacology.org/, (Armstrong et al., 2020)], KEGG DRUG [https://www.kegg.jp/kegg/drug/, (Kanehisa et al., 2019)], and Metabolism and Transport Database [http://www-metrabase.ch.cam.ac.uk/, (Mak et al., 2015)] offered millions of molecules that were paired with the ADME-associated proteins. As shown in Fig. 1, all these databases focused on the data of exogenous substances and their regulation (colored in green), especially the data of regulatory substances and the inhibitors/inducers of a studied DT (as shown in Table 2). Moreover, all the databases described the DTs of the approved/clinical trial drugs, and the number of DTs covered by these six databases varied greatly (from ~10 to over 100, as shown in Table 1). Among these databases, the Therapeutic Target Database and Metrabase were the only two describing the tissue-specific distribution of DTs, and such data could facilitate the critical analysis of distribution-induced adverse drug reactions (Yang et al., 2016).

PharmGKB [https://www.pharmgkb.org/, (Barbarino et al., 2018)] is a worldwide resource for pharmacogenomics knowledge that provides the alteration data of drug pharmacokinetics and pharmacodynamics that originate from genetic polymorphism. It focuses on the alterations in drug response and the effects on their clinical phenotypes and contains ~1,000 drugs related to the genetic variations on ~100 DTs. As shown in Fig. 1, in addition to the exogenous regulation data, PharmGKB offered additional DT data on expression/distribution/function and genetic polymorphism. Compared with the databases above, PharmGKB offered many diverse groups of DT data (Table 2) by describing functional family, cytogenetic location, disease/phenotype induced by the hereditary factor together with the genetic variant and frequency.

UCSF-FDA TransPortal [https://transportal.compbio.ucsf.edu/, (Morrissey et al., 2012)] and Transformer [http://bioinformatics.charite.de/transformer, (Hoffmann et al., 2014)] were two popular databases providing important drug transporters together with the exogenous substance and regulation, which contain 31 and 60 DTs for transporting approved or in clinical trial drugs, respectively. As demonstrated in Fig. 1 and Table 2, UCSF-FDA TransPortal described the tissue-specific distribution information of DTs, whereas Transformer offered distinctive data on species-specific structural evolution and the three-dimensional crystal structure of the entire transporter. Moreover, as shown in Table 2, these two databases are distinguished in covering the data of clinical DDI and are therefore applied to predict potential adverse drug reactions based on their DDI data (Cesar-Razquin et al., 2018; Carrascal-Laso et al., 2020). It is important to emphasize that the latest update of UCSF-FDA TransPortal was in 2012.

As a recently constructed pharmaceutical database, VARIDT [https://idrblab.org/varidt/, (Yin et al., 2020)] offered the most comprehensive set of DTs that were confirmed by the transporting drugs (either approved or clinical trial). As shown in Fig. 1, this database contained the most diverse types of DT-related data (with the only exception of structure-based data). As described in Table 2, the data for all data

TABLE 1

Summary of the data completeness of DT and its corresponding drugs, data availability, developer, updating frequency of the databases included in this review
The "" in the first column indicated that the data provided in the corresponding databases were primarily based on computational calculation or simulation, whereas the databases without "*" represented that their data were manually collected from scientific literatures that were based on experimental validations.*

Database	Year of Latest/First Release	No. of DTs (Drugs)	Developer	Updating Frequency	Data Batch Download	Official Website of the Database
Databases with Its First Version Published in Recent Five Years						
ABCA4 database	2017 / 2017	1 (0)	Jack Brockhoff Foundation	(first version)	NO	http://www.sbl.unisi.it/abca4/
iMusta4SLC*	2018 / 2018	∼220 (0)	BINDS	(first version)	YES	http://cib.cf.ocha.ac.jp/slc/
PPTdb*	2019 / 2019	∼80 (0)	Chang Gung University	(first version)	YES	http://pptdb.cgu.edu.tw
VARIDT	2020 / 2020	266 (886)	Zhejiang University	(first version)	YES	https://idrblab.org/varidt/
Databases Published before and Keeping Update in Recent Five Years						
ABCMdb	2017 / 2012	36 (0)	Hungarian Academy of Science	5 Years	NO	http://abcm2.hegelab.org/
ChEMBL	2019 / 2012	124 (∼800)	EMBL-EBI	2 Years	YES	https://www.ebi.ac.uk/chembl/
DrugBank	2018 / 2006	136 (∼800)	Genome Alberta	2 Years	YES (*need registration*)	https://go.drugbank.com/
EBI Expression Atlas	2020 / 2010	∼250 (0)	EMBL-EBI	4 Years	YES	https://www.ebi.ac.uk/gxa/
EncoMPASS	2019 / 2018	∼40 (∼10)	NINDS/NIH	1 Year	YES	http://encompass.ninds.nih.gov
FINDbase	2020 / 2007	25 (0)	GoldenHelix Fundtion	3 Years	NO	http://www.findbase.org
IUPHAR/BPS	2020 / 2009	22 (∼70)	NC-IUPHAR	2 Years	YES	https://www.guidetopharmacology.org/
KEGG DRUG	2019 / 1999	14 (∼150)	Kyoto University	1 Year	NO	https://www.kegg.jp/kegg/drug/
OMIM	2019 / 1995	∼200 (0)	NHGRI	1 Year	YES (*need registration*)	https://omim.org/
PDB	2021 / 2000	∼60 (∼20)	NSF/NIH	1 Year	YES	https://www.rcsb.org/
PharmGKB	2018 / 2002	∼100 (∼800)	NIH/NHGRI/NICHD	6 Years	YES	https://www.pharmgkb.org/
MemProtMD*	2019 / 2015	∼20 (0)	University of Oxford	4 Years	YES	http://memprotmd.bioch.ox.ac.uk/
TCDB	2021 / 2006	266 (0)	NIH	5 Years	YES	https://www.tcdb.org/
TransportDB*	2017 / 2004	∼250 (0)	Macquarie University	10 Years	YES	http://www.membranetransport.org/
TTD	2020 / 2002	∼100 (∼700)	Zhejiang University	2 Years	YES	https://idrblab.org/ttd/
UniProt	2021 / 2004	266 (∼100)	NIH	1 Year	YES	https://www.uniprot.org/
Databases Published before 2016 and without Any Update in Recent Five Years						
ALD Info	2001 / 2001	1 (0)	University of Amsterdam	(first version)	YES	https://adrenoleukodystrophy.info/
CFMD	2011 / 2011	1 (0)	US CF Foundation	(first version)	NO	http://www.genet.sickkids.on.ca/cftr/
dbSNP	2001 / 1999	∼250 (0)	NLM	1 Year	YES	https://www.ncbi.nlm.nih.gov/snp/
Metrabase	2015 / 2015	20 (∼500)	University of Cambridge	(first version)	YES	http://www-metrabase.ch.cam.ac.uk/
METscout	2013 / 2013	∼200 (0)	Max Planck Society	(first version)	NO	http://metscout.mpg.de/
SLC TABLES	2013 / 2013	∼220 (0)	University of Bern	(first version)	NO	http://slc.bioparadigms.org/
The Human Protein Atla	2015 / 2015	∼250 (0)	Knut and Alice Foundation	(first version)	YES	https://www.proteinatlas.org/
Transformer	2014 / 2010	60 (∼250)	Universitätsmedizin Berlin	4 Years	NO	http://bioinformatics.charite.de/transformer
UCSF-FDA TransPortal	2012 / 2012	31 (∼480)	FDA Critical Path Initiative	(first version)	NO	https://transportal.compbio.ucsf.edu/

BINDS, basis for supporting innovative drug discovery and life science research; EMBL-EBI, European bioinformatics institute; NC-IUPHAR, nomenclature and standards committee of international union of clinical pharmacology; NHGRI, national human genome research institute; NIH, National Institutes of Health; NICHD, National Institute of Child Health and Human Development; NINDS: National Institute of Neurologic Disorders and Stroke; NLM, National Library of Medicine; NSF, National Science Foundation; US CF Foundation: Cystic fibrosis foundation.

groups under four different types were collected and provided. Moreover, the total number of DTs covered in this database was the largest compared with those knowledge bases in Fig. 1. In particular, a comprehensive literature review of all drugs approved by the FDA and ∼1,100 clinical trial drugs were first conducted. Then, a total of ∼180 DTs were confirmed to transport approved drugs, and ∼150 DTs were to transport clinical trial ones, which were substantially different from the relatively small numbers of DTs shown in available databases

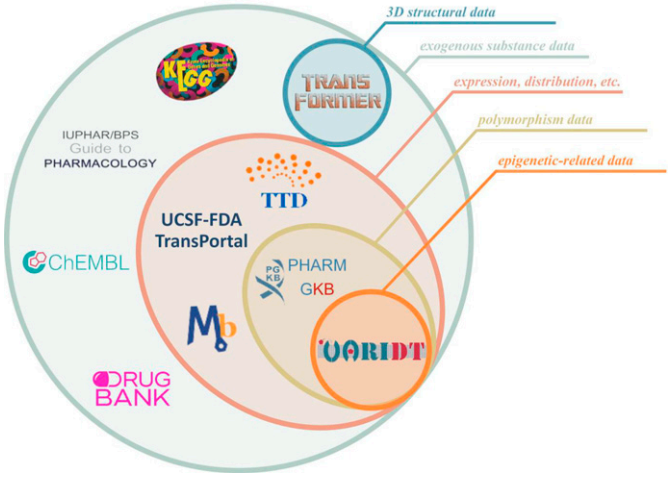

Fig. 1. Ten representative databases providing the information of drugs together with the corresponding DTs. Five types of DT-related data were shown in the circles with various colors, including 3D structure, endogenous substrates, expression/distribution/function, polymorphism, and epigenetic-related data.

(Table 2). Due to the huge amount of accumulated DT data, the VARIDT is expected to provide strong support to the optimization of clinical treatment.

Diverse Data Illustrating Various Aspects of DT Variability. The variability data of DTs are essential for the determination of the interindividual variations in drug response and side effects (Yee et al., 2018; Nie et al., 2020). Besides the variabilities in exogenous regulation and genetic polymorphism explicitly discussed in the 2.1 section, two additional aspects of variability (varied protein abundances and diverse epigenetic regulation) should be considered for DTs because of their importance in bridging the preclinical investigations with clinical trials (Durmus et al., 2015) and leading to multidrug resistance in complex disease (Zhou et al., 2020), respectively. Therefore, current databases available for providing these two additional variability data were explicitly described in this review as follows.

The protein abundance of DTs plays an important role in several aspects of drug research, such as clinical toxicity analysis, clinical pharmacokinetics research, and adverse reaction evaluation (Lin et al., 2015; Safar et al., 2019). There are three kinds of variability of DT abundances: 1) organism-specific expressions (Durmus et al., 2015), 2) tissue-differential distributions (Nixon et al., 2016), and 3) disease-dependent abundances (Evers et al., 2018). As provided in Table 2, the tissue-differential distribution data have been provided by multiple databases, such as TTD, PharmGKB, UCSF-FDA TransPortal, Metrabase, and VARIDT, which further demonstrate the critical roles of such variability in drug disposition (Kawahara et al., 2020). For the remaining two kinds of variability data, VARIDT is the only knowledge base of such information, and the differential expression patterns are provided for 108 diseases and 3 model organisms.

Epigenetic regulation of DT genes has emerged as an important mechanism of individualized drug responses (Peng and Zhong, 2015; Hirota et al., 2017). Few epigenetic regulation data of DTs (Table 2) are provided by currently available knowledge bases, and the VARIDT is currently the only resource describing such variability. Particularly, it provided epigenetic regulation data on 1) epigenetic types (DNA methylation, non-coding RNA regulation, histone acetylation/methylation, etc.), 2) prevalence of occurrence, 3) locations, 4) description of the epigenetic phenomenon, 5) experimental methods,

TABLE 2

The availability of DT-related data types and groups among those ten databases (shown in Fig. 1) that provided the information of drugs and their corresponding transporters (DTs)

'√' indicated that the data type is available, whereas '–' denotes that the data type is not available.

		ChEMBL	DrugBank	TTD	IUPHAR BPS	PharmGKB	KEGG	UCSF-FDA TransPortal	Trans former	Metrabase	VARIDT
Expression, Distribution, and Function Data of DTs	Disease-Varied Expression	–	–	–	–	–	–	–	–	–	√
	Organism-Specific Abundance	–	–	–	–	–	–	–	–	–	√
	Protein Functional Family	–	–	–	–	√	–	–	–	–	√
	Protein Sequence Information	–	–	–	–	–	–	–	–	–	√
	Tissue-Differential Distribution	–	–	√	–	√	–	√	–	√	√
Polymorphism Data of DTs	Cytogenetic Location Information	–	–	–	–	√	–	–	–	–	√
	Genetically Correlated Phenotype	–	–	–	–	√	–	–	–	–	√
	Genetic Variant and Frequency	–	–	–	–	√	–	–	–	–	√
	Genetically Induced Disease	–	–	–	–	√	–	–	–	–	√
Structure-related Data of DTs	Species-Specific Evolution	–	–	–	–	–	–	–	√	–	–
	Whole Protein Structure	–	–	–	–	–	–	–	√	–	–
Epigenetic Data of DTs	DNA/histone Methylation Acetylation	–	–	–	–	–	–	–	–	–	√
	Noncoding RNA Regulation	–	–	–	–	–	–	–	–	–	√
Exogenous Substances of DTs	Clinical Drug-drug Interaction	–	–	–	–	–	–	√	√	–	√
	Exogenous Regulatory Substrates	√	√	√	√	√	√	√	√	√	√
	Transporter Inhibitor and Inducer	√	√	√	√	√	√	√	√	√	√

and 6) materials adopted for validating each phenomenon. In total, over 20,000 DNA methylations, ~100 histone modifications, and over 7,000 noncoding RNA regulations were collected and comprehensively provided in the latest VARIDT.

Databases Describing Transporters and Transporter Families

Membrane transporters play critical roles in discovering new drugs and elucidating disease mechanisms (Nigam, 2018), which can be divided into channels, carriers, electron flow carriers, group translocators, and pumps for determining the molecular composition and energy state of cells (Cook et al., 2014; Saier et al., 2021). The identified drug uptake/efflux transporters may constitute only a small fraction of all these general transporters, but these general transporters are of great importance for elucidating drug metabolism (Wang et al., 2020b) and disposition (Kawahara et al., 2020). Thus, the databases available for describing general transporters and transporter families are valuable treasures for current DT research.

These databases include TCDB (Saier et al., 2021), METscout (Geffers et al., 2013), CFMD (Sosnay et al., 2011), iMusta4SLC (Higuchi et al., 2018), ABCMdb (Tordai et al., 2017), ALD info (Kemp et al., 2001), ABCA4 DataBase (Trezza et al., 2017), TransportDB (Elbourne et al., 2017), and SLC Tables (Hediger et al., 2013), which contain the data on classifying general transporters or describing a specific class of proteins. Such data provided the resources for the expansion of DT-related knowledge, which was described in many databases (as illustrated in Fig. 2), and a variety of distinct data groups covered by these popular databases were also comprehensively reviewed and discussed in Table 3.

Systematic Classification of the General Protein Transporters. TCDB [https://www.tcdb.org/, (Saier et al., 2021)] is a well established database for classifying general protein transporters. It contains transporter information of diverse species and describes the general transporter in terms of structure, function, mechanism, evolution, disease/medicine, and related endogenous compounds (Fig. 2 and Table 3). Collectively, this database covered over 20,000 transporters classified into thousands of nonredundant function families, and it enables the assessments of the family members, the discovery of their evolutionary relationships, and inference of substrate and molecular functions. It has been adopted recently for optimizing experimental designs (Hong et al., 2020; Wang et al., 2020b; Yang et al., 2020a; Graf et al., 2021; Peng et al., 2021).

TransportDB [http://www.membranetransport.org/transportDB2/, (Elbourne et al., 2017)] is a functional annotation database containing information on a wide range of transporters derived from diverse species. Particularly, it annotates membrane transporters from ~2,000 genomes and results in ~800,000 transporters grouped into ~160 families. As shown in Fig. 2, this database contained the data of expression, distribution, function, and endogenous substrates for general transporter, which gives functional family, transporter phylogenetic classification, and structure of endogenous compounds (Table 3). TransportDB was suggested to be adopted for characterizing transporters of specific functions (Frioux et al., 2020; Bernstein et al., 2021).

Knowledge Bases Describing a Specific Transporter Family. SLC Tables [http://slc.bioparadigms.org/, (Hediger et al., 2013)] is a database with specific data on ~400 absolute carriers (SLCs) classified into 52 functional families. This database is popular for describing detailed data on the functional family, endogenous substances, and tissue-differential distribution (Fig. 2 and Table 3). Because of its specific scope of describing the SLC transporter family, it has been frequently used to facilitate SLC-related studies (Girardi et al., 2020). As another SLC-centered database, the METscout [http://metscout.mpg.de/, (Geffers et al., 2013)] provides the metabolic pathway and gene expression landscape, which describe where in an organism each metabolic reaction takes place and where the SLCs transport the metabolites. It contains ~350 SLCs and covers almost all components within the mouse metabolic network. As illustrated in Fig. 2, it provides the functional family, organism-specific abundance, tissue-differential distribution of transporters, together with the scRNA sequencing atlas (described in Table 3).

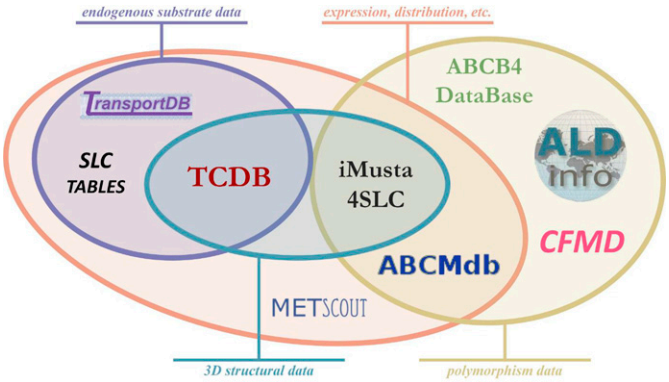

Fig. 2. Nine representative databases describing the information of transporters and transporter families. Four types of transporter-related data were shown in the circles with various colors, including endogenous substrates, expression/distribution/function, structure, and polymorphism-related data.

Other databases for a specific transporter family include: ABCMdb [http://abcm2.hegelab.org/, (Trezza et al., 2017)] and iMusta4SLC [http://cib.cf.ocha.ac.jp/slc/, (Higuchi et al., 2018)]. Both knowledge bases focus on providing the genetic mutation information for a particular family of transporters (shown in Fig. 2). ABCMdb has 45 ABC transcripts classified into 5 families, and iMusta4SLC provides 573 SLC transcripts classified into 52 families. Both databases can predict potential disease liability based on the mutations in a general transporter and can help to develop extensive disease knowledge networks for improving disease management (Verkman et al., 2013; Tracewska et al., 2019; Chien et al., 2021).

Knowledge Bases Describing a Specific Transporter. A number of additional knowledge bases were constructed to describe genetic polymorphisms for specific transporter, which included CFMD [http://www.genet.sickkids.on.ca/cftr/, (Sosnay et al., 2011)], ALD Info [https://adrenoleukodystrophy.info/, (Kemp et al., 2001)], and ABCA4 DataBase [http://www.sbl.unisi.it/abca4/abcr_mainlist.php, (Trezza et al., 2017)]. As indicated by their name, these knowledge bases contain information on only a single transporter, such as CFTR1, ABCD1, and ABCA4. Particularly, they provided comprehensive disease data that were associated with the sequential/structural polymorphism of a transporter. As illustrated in Fig. 2 and Table 3, CFMD contains the data of cytogenetic locations and genetic variants and frequency, ALD Infor provides the data of genetically induced disease indications, and ABCA4 DataBase includes the data of genetically correlated phenotypes.

Databases Providing Transporters as Part of Their Data Collection

With the advancement of next-generation sequencing techniques (Lane et al., 2016; Yin et al., 2021), many protein-coding genes have been successfully characterized. In addition to the databases discussed above, some knowledge bases describing the whole protein atlas were also available. Within these databases, the transporters were described as a part of their entire data collection. Specifically, these databases included: dbSNP, EBI Expression Atlas, EncoMPASS, FINDbase, Human Protein Atlas, OMIM, PDB, PPTdb, membrane proteins embedded in lipid bilayers database, and UniProt. These databases focus on

TABLE 3

The availability of transporter-related data types and groups among those nine databases (shown in Fig. 2) that described the information of transporters and transporter families

'√' indicated that the data type is available, whereas '–' denotes that the data type is not available.

		TCDB	SLC TABLES	TransportDB	METscout	CFMD	ALD Info	ABCA4 DataBase	ABCMdb	iMusta4SLC
Expression, Distribution, and Function Data of DTs	Disease-Varied Expression	–	–	–	–	–	–	–	–	√
	Organism-Specific Abundance	–	–	–	√	–	–	–	–	–
	Protein Functional Family	√	√	√	√	–	–	–	–	–
	Protein Sequence Information	–	–	–	√	–	–	–	√	–
	Phylogenetic Classification System	√	–	√	–	–	–	–	–	–
	Tissue-Differential Distribution	–	√	–	√	–	–	–	–	–
	scRNA Sequencing Atlas	–	–	–	√	–	–	–	–	–
Genetic Polymorphism Data of DTs	Cytogenetic Location Information	–	–	–	–	√	–	–	√	√
	Genetically Correlated Phenotype	–	–	–	–	–	–	√	–	√
	Genetic Variant and Frequency	–	–	–	–	√	√	–	√	–
	Genetically Induced Disease	–	–	–	–	–	√	–	–	√
Structural Data of DTs	Species-Specific Evolution	√	–	–	–	–	–	–	–	–
	Whole Protein Structure	–	–	–	–	–	–	–	–	√
Endogenous Substances of DTs	Substrate Functional Family	√	√	–	–	–	–	–	–	–
	Substrate Structure Information	√	√	√	–	–	–	–	–	–
	Substrate Transporting Mechanism	√	√	–	–	–	–	–	–	–

macroscopic and comprehensive descriptions of all proteins, and the information on all transporters is therefore provided in a generally described manner.

As shown in Fig. 3, three types of transporter-related data were provided in these databases. For the data of genetic polymorphism, three databases were available, which included: dbSNP [https://www.ncbi.nlm.nih.gov/snp/, (Sherry et al., 2001)], FINDbase [http://www.findbase.org, (Kounelis et al., 2020)], and OMIM [https://omim.org/, (Amberger et al., 2019)]. As described in Table 4, all three databases illustrated the genetic variant and frequency information of the studied transporters, with OMIM being the only source for tissue-specific distribution, genetically correlated phenotype, and cytogenetic location. For the data of expression, distribution, and function, three popular databases were available, which included: UniProt [https://www.uniprot.org/, (UniProt, 2021)] and the Human Protein Atlas [https://www.proteinatlas.org/, (Uhlen et al., 2015)] together with EBI Expression Atlas [https://www.ebi.ac.uk/gxa/home, (Papatheodorou et al., 2020)]. Based on the descriptions in Table 4, all three databases focus on tissue-differential distribution and organism-specific abundance. UniProt provided the comprehensive information on functional families and transporter sequences, whereas EBI Expression Atlas places more emphasis on disease-varied expression. Among these three databases, the Human Protein Atlas has the widest coverage on the transporter data groups as described in Table 4. For the data of structural conformation, four reputable databases were available, which included: PDB [https://www.rcsb.org/, (Burley et al., 2021)], EncoMPASS [http://encompass.ninds.nih.gov, (Sarti et al., 2019)], membrane proteins embedded in lipid bilayers database [http://memprotmd.bioch.ox.ac.uk/, (Newport et al., 2019)], and PPTdb [http://pptdb.cgu.edu.tw, (Lee et al., 2019)]. As described in Table 4, all four databases provided structural conformation for the entire transporter (if available). As the most comprehensive database for protein crystal structures, PDB also described the substrate-binding domain of transporter with relatively high resolution. PPTdb had more data groups (Table 4) and gave the unique data on species-specific evolution and the structure of functionally conserved domain.

Customized Database Functions Facilitating DT-related Research

Besides the valuable DT-related data, a variety of customized functions facilitating DT-related research were also provided in several databases. These functions included sequence-based DT similarity screening (Elbourne et al., 2017), structure-based similarity screening for transported drug (Mendez et al., 2019), disease/tissue-specific differential expression analysis (Uhlen et al., 2015), interplay analysis among multiple DT variabilities (Yin et al., 2020), functional analysis

Fig. 3. Ten representative databases providing transporter information as part of their data collections. These databases included the transporter information of three types which were shown by the circles of different colors, including expression/distribution/function data, polymorphism data, and 3D structure.

TABLE 4

The availability of data types and groups among the ten databases (shown in Fig. 3) that provided the transporter-related information as part of their data collections
'√' indicated that the data type is available, whereas '–' denotes that the data type is not available.

		dbSNP	FINDbase	OMIM	UniProt	The Human Protein Atlas	EBI Expression Atlas	PDB	EncoMPASS	PPTdb	MemProMD
Expression, Distribution, and Function Date of DTs	Disease-Varied Expression	–	–	–	–	√	√	–	–	–	–
	Organism-Specific Abundance	–	–	–	√	√	√	–	–	–	–
	Protein Functional Family	–	–	√	√	√	–	–	–	√	–
	Protein Sequence Information	–	–	–	√	√	–	–	–	–	–
	Tissue-Differential Distribution	–	–	√	√	√	√	–	–	–	–
	scRNA Sequencing Atlas	–	–	–	–	√	–	–	–	–	–
Polymorphism Data of DTs	Cytogenetic Location Information	–	–	√	–	–	–	–	–	–	
	Genetically Correlated Phenotype	–	–	√	–	–	–	–	–	–	–
	Genetic Variant and Frequency	√	√	√	–	–	–	–	–	–	–
	Genetically Induced Disease	–	√	√	–	–	–	–	–	–	–
Structure-related Data of DTs	Functional Conserved Domains	–	–	–	√	–	–	–	–	√	–
	Species-Specific Evolution	–	–	–	–	–	–	–	–	√	–
	Substrate-Binding Domain	–	–	–	–	–	–	√	–	√	–
	Whole Protein Structure	–	–	–	√	–	–	√	√	√	√

based on signaling pathways (Kanehisa et al., 2019), DT annotation and classification (Saier et al., 2021), and so on. Based on these valuable functions together with their comprehensive DT-related information, the available databases provided much-enhanced power in the research of drug metabolism and disposition. As shown in Table 5, these functions facilitated the structure-based drug design/identification (Yu et al., 2016), discovery of target drugability based on DT sequence (Frioux et al., 2020), disease/tissue-specific differential expression analysis (Yu et al., 2020), structure similarity search by the transported drug (Sakai et al., 2021), interplay analysis among multiple DT variabilities (Wang et al., 2021), functional analysis based on the signaling pathways (Sakil et al., 2017), functional annotation and systematic classification of DTs (Peng et al., 2021), prediction of potential DDIs (Carrascal-Laso et al., 2020), drug safety assessment and toxicity discovery (Zhou et al., 2020), and identification of potential drug resistance (Hlaváč et al., 2020). Overall, these customized database functions are very diverse, which are capable of promoting DT-based research on the drug ADME process.

Summary and Prospect.

Based on the above discussions, the available databases are useful for translating experimental results into clinical evidence, which can enable clinicians to formulate appropriate medications for a specific patient and provide qualified solutions for drug discovery. Recent studies showed that there is an increasing interest in the variability of DTs, which emphasized the importance of 1) epigenetic regulation and genetic polymorphism of DT, 2) species-, tissue-, and disease-specific DT abundances, and 3) exogenous factors modulating DT activity (Yin et al., 2020). These data have been provided by some available databases, such as PharmaGKB (Barbarino et al., 2018), UCSF-FDA TransPortal (Morrissey et al., 2012), and Transformer (Hoffmann et al., 2014), and each database focuses on one particular aspect of DT variability.

Recent studies revealed the urgent necessity of conducting interplay analysis among multiple aspects of DT variability (Chen et al., 2016; Genovese et al., 2017; Ye et al., 2018; Yang et al., 2020b, 2020c). Taking the multidrug resistance as an example, the impaired uptake of organic cation transporter 1 (hOCT1) was found responsible for the chemoresistance of sorafenib in treating the cholangiocarcinoma. The decrease of the hOCT1 mRNA level was identified to be correlated with the hypermethylation status of its promoter, and treatment of cholangiocarcinoma cells with decitabine (a demethylating agent) was found to be able to restore hOCT1's expression and increase the uptake of sorafenib (Lozano et al., 2019). This example explicitly demonstrates an interplay between (1) epigenetic regulation of DT and (2) exogenous regulation modulating DT activity.

Similar to hOCT1, organic anion transporter 2 (hOAT2) is another hotspot in current research, and its aberrant expression was reported to lead to insufficient intracellular drug accumulation, which is responsible for the failure of chemotherapy in the patient with hepatocellular carcinoma. The transcriptional repression of hOAT2 is associated with histone deacetylations, and the activation of hOAT2's transcription and enhanced uptake of the OAT2 substrate zidovudine can thus be achieved by histone deacetylases inhibitor Vorinostat (Wang et al., 2021). All in all, the joint consideration of multiple DT variabilities (in this situation, epigenetic regulation and exogenous chemicals) can help to discover potential chemo-sensitization strategies for treating cancers. Such valuable information has been provided in the latest version of VARIDT.

Finally, with the advent of the big-data era, the available pharmaceutical knowledge bases are expected to be fully connected to avoid the problem of "information isolated islands" (Fu et al., 2020). A careful review of all those discussed databases above-identified several reputable databases that were fully connected with other available knowledge bases,

TABLE 5

The customized functions of all 29 databases discussed in this study and their representative applications. These functions fall into three classes: facilitating the rational use of drugs, discovering the potential therapeutic targets, and developing the new strategy for disease treatment

Class of Function	Customized Function of Each Analyzed Database	Typical Database(s)	Representative Applications of These Databases
Discovering the Potential Therapeutic Targets	Structure-based Drug Design or Identification	PDB PPTdb MemProt MD	PDB database was used to identify a novel AQP4 inhibitor binding deep inside this transporter based on the molecular dynamics using a high-resolution crystal AQP4 structure (Yu et al., 2016).
	Sequence-based Discovery of Target Druggability	TransportDB TTD TCDB	TransportDB database was adopted for predicting transporters from the genome and providing a breakthrough for the functional annotation of a large number of transporters (Frioux et al., 2020).
	Disease-specific Differential Expression Analysis	Human Protein Atlas EBI Expression Atlas VARIDT	Human Protein Atlas was used to extract the expression pattern of SLC16A1 and SLC16A3 for their clinical potential applications in the treatment of pancreatic adenocarcinoma (Yu et al., 2020).
	Structure Similarity Search by Transported Drugs	ChEMBL TTD DrugBank	ChEMBL database was used to identify a new inhibitor of serotonin transporter with comparable affinity to the commercial drug by structure similarity search and virtual screening (Sakai et al., 2021).
Developing the New Strategy for Disease Treatment	Interplay Analysis among Multiple DT Variabilities	VARIDT	VARIDT database was used to facilitate the interplay analysis of OAT2 in hepatocellular carcinoma between its disease-specific differential expression and histone acetylation (Wang et al., 2021).
	Functional Analysis Based on Signaling Pathways	KEGG PharmGKB	KEGG database was applied to identify the key transporter pathways involving in the development of breast cancer (Sakil et al., 2017) and the microgravity effects in epidermal stem cells (Li et al., 2020a).
	Functional Annotation and Systematic Classification	TCDB	TCDB database was adopted to facilitate the functional annotation and systematic classification of DT using its transporter automatic annotation pipeline (Graf et al., 2021; Peng et al., 2021).
Facilitating the Rational Use of Drugs	Prediction of DT-based Potential DDI	Transformer UCSF-FDA TransPortal PharmGKB	Transformer database was adopted to predict the potential DDIs for reducing the costs in novel drug development and optimizing the process of rational drug design (Carrascal-Laso et al., 2020)
	Drug Safety Assessment and Toxicity Prediction	Human Protein Atlas VARIDT EBI Expression Atlas	VARIDT was applied to reveal the biologic mechanism of bile acids efflux using the tissue-specific expression of two subunits of organic solute transporter in ileum (Zhou et al., 2020).
	Identification of Potential Drug Resistance	PharmGKB OMIM iMusta4SLC	PharmGKB database was used to predict the response of drugs in cancer treatment based on the pharmacogenomic analysis focusing on ATP binding cassette transporters (Hlaváč et al., 2020).

such as: ChEMBL, DrugBank, Therapeutic Target Database, PharmGKB, VARIDT, and so on. However, there are still some databases that are not fully linked to other information resources. To promote the publicity of these databases and truly demonstrate the capacity of big-data analysis, the global scientific community should strive together to build a comprehensive database that includes integral information on DTs and their variabilities. This comprehensive database may facilitate the discovery of the correlation between disease/adverse drug reaction and the studied DT.

Authorship Contributions

Participated in research design: Zhu, Zeng.
Performed data analysis: Yin, F. Li, Z. Li, Yu.
Wrote or contributed to the writing of the manuscript: Yin, Zhu, Zeng.

References

Amberger JS, Bocchini CA, Scott AF, and Hamosh A (2019) OMIM.org: leveraging knowledge across phenotype-gene relationships. *Nucleic Acids Res* **47** (D1):D1038–D1043.

Armstrong JF, Faccenda E, Harding SD, Pawson AJ, Southan C, Sharman JL, Campo B, Cavanagh DR, Alexander SPH, Davenport AP, et al.; NC-IUPHAR (2020) The IUPHAR/BPS guide to pharmacology in 2020: extending immunopharmacology content and introducing the IUPHAR/MMV guide to malaria pharmacology. *Nucleic Acids Res* **48** (D1):D1006–D1021.

Bai X, Chen Y, Hou X, Huang M, and Jin J (2016) Emerging role of NRF2 in chemoresistance by regulating drug-metabolizing enzymes and efflux transporters. *Drug Metab Rev* **48**:541–567.

Barbarino JM, Whirl-Carrillo M, Altman RB, and Klein TE (2018) PharmGKB: A worldwide resource for pharmacogenomic information. *Wiley Interdiscip Rev Syst Biol Med* **10**:e1417.

Bernstein DB, Sulheim S, Almaas E, and Segrè D (2021) Addressing uncertainty in genome-scale metabolic model reconstruction and analysis. *Genome Biol* **22**:64.

Burley SK, Bhikadiya C, Bi C, Bittrich S, Chen L, Crichlow GV, Christie CH, Dalenberg K, Di Costanzo L, Duarte JM, et al. (2021) RCSB protein data bank: powerful new tools for exploring 3D structures of biological macromolecules for basic and applied research and education in fundamental biology, biomedicine, biotechnology, bioengineering and energy sciences. *Nucleic Acids Res* **49** (D1):D437–D451.

Carrascal-Laso L, Franco-Martín MA, García-Berrocal MB, Marcos-Vadillo E, Sánchez-Iglesias S, Lorenzo C, Sánchez-Martín A, Ramos-Gallego I, García-Salgado MJ, and Isidoro-García M (2020) Application of a pharmacogenetics-based precision medicine model (5SPM) to psychotic patients that presented poor response to neuroleptic therapy. *J Pers Med* **10**:289.

César-Razquin A, Girardi E, Yang M, Brehme M, Saez-Rodriguez J, and Superti-Furga G (2018) In silico prioritization of transporter-drug relationships from drug sensitivity screens. *Front Pharmacol* **9**:1011.

Chen Z, Shi T, Zhang L, Zhu P, Deng M, Huang C, Hu T, Jiang L, and Li J (2016) Mammalian drug efflux transporters of the ATP binding cassette (ABC) family in multidrug resistance: a review of the past decade. *Cancer Lett* **370**:153–164.

Chien CY, Chang KH, and Chen CM (2021) X-linked adrenoleukodystrophy caused by a novel mutation presenting with various phenotypes in a Taiwanese family. *Clin Chim Acta* **514**:100–106.

Cook GM, Greening C, Hards K, and Berney M (2014) Energetics of pathogenic bacteria and opportunities for drug development. *Adv Microb Physiol* **65**:1–62.

DeGorter MK, Xia CQ, Yang JJ, and Kim RB (2012) Drug transporters in drug efficacy and toxicity. *Annu Rev Pharmacol Toxicol* **52**:249–273.

Dias PJ and Sá-Correia I (2014) Phylogenetic and syntenic analyses of the 12-spanner drug:H(+) antiporter family 1 (DHA1) in pathogenic Candida species: evolution of MDR1 and FLU1 genes. *Genomics* **104**:45–57.

Durmus S, Lozano-Mena G, van Esch A, Wagenaar E, van Tellingen O, and Schinkel AH (2015) Preclinical mouse models to study human OATP1B1- and OATP1B3-mediated drug-drug interactions in vivo. *Mol Pharm* **12**:4259–4269.

Elbourne LD, Tetu SG, Hassan KA, and Paulsen IT (2017) TransportDB 2.0: a database for exploring membrane transporters in sequenced genomes from all domains of life. *Nucleic Acids Res* **45** (D1):D320–D324.

Evers R, Piquette-Miller M, Polli JW, Russel FGM, Sprowl JA, Tohyama K, Ware JA, de Wildt SN, Xie W, and Brouwer KLR; International Transporter Consortium (2018) Disease-associated changes in drug transporters may impact the pharmacokinetics and/or toxicity of drugs: a white paper from the international transporter consortium. *Clin Pharmacol Ther* **104**:900–915.

Frioux C, Singh D, Korcsmaros T, and Hildebrand F (2020) From bag-of-genes to bag-of-genomes: metabolic modelling of communities in the era of metagenome-assembled genomes. *Comput Struct Biotechnol J* **18**:1722–1734.

Fu J, Wang N, and Cai Y (2020) Privacy-preserving in healthcare blockchain systems based on lightweight message sharing. *Sensors (Basel)* **20**:1898.

Garibsingh RA and Schlessinger A (2019) Advances and challenges in rational drug design for SLCs. *Trends Pharmacol Sci* **40**:790–800.

Geffers L, Tetzlaff B, Cui X, Yan J, and Eichele G (2013) METscout: a pathfinder exploring the landscape of metabolites, enzymes and transporters. *Nucleic Acids Res* **41**:D1047–D1054.

Genovese I, Ilari A, Assaraf YG, Fazi F, and Colotti G (2017) Not only P-glycoprotein: amplification of the ABCB1-containing chromosome region 7q21 confers multidrug resistance upon cancer cells by coordinated overexpression of an assortment of resistance-related proteins. *Drug Resist Updat* **32**:23–46.

Giacomini KM, Huang SM, Tweedie DJ, Benet LZ, Brouwer KL, Chu X, Dahlin A, Evers R, Fischer V, Hillgren KM, et al.; International Transporter Consortium (2010) Membrane transporters in drug development. *Nat Rev Drug Discov* **9**:215–236.

Girardi E, Agrimi G, Goldmann U, Fiume G, Lindinger S, Sedlyarov V, Srndic I, Gürtl B, Agerer B, Kartnig F, et al. (2020) Epistasis-driven identification of SLC25A51 as a regulator of human mitochondrial NAD import. *Nat Commun* **11**:6145.

Graf JS, Schorn S, Kitzinger K, Ahmerkamp S, Woehle C, Huettel B, Schubert CJ, Kuypers MMM, and Milucka J (2021) Anaerobic endosymbiont generates energy for ciliate host by denitrification. *Nature* **591**:445–450.

He Y, Lian W, Ding L, Fan X, Ma J, Zhang QY, Ding X, and Lin G (2021) Lung injury induced by pyrrolizidine alkaloids depends on metabolism by hepatic cytochrome P450s and blood transport of reactive metabolites. *Arch Toxicol* **95**:103–116.

Hediger MA, Clémençon B, Burrier RE, and Bruford EA (2013) The ABCs of membrane transporters in health and disease (SLC series): introduction. *Mol Aspects Med* **34**:95–107.

Higuchi A, Nonaka N, and Yura K (2018) iMusta4SLC: Database for the structural property and variations of solute carrier transporters. *Biophys Physicobiol* **15**:94–103.

Hirota T, Tanaka T, Takesue H, and Ieiri I (2017) Epigenetic regulation of drug transporter expression in human tissues. *Expert Opin Drug Metab Toxicol* **13**:19–30.

Hitchings R and Kelly L (2019) Drug metabolism as a community effort. *Cell Metab* **30**:235–237.

Hlaváč V, Holý P, and Souček P (2020) Pharmacogenomics to predict tumor therapy response: a focus on ATP-binding cassette transporters and cytochromes P450. *J Pers Med* **10**:108.

Hoffmann MF, Preissner SC, Nickel J, Dunkel M, Preissner R, and Preissner S (2014) The transformer database: biotransformation of xenobiotics. *Nucleic Acids Res* **42**:D1113–D1117.

Hong J, Luo Y, Zhang Y, Ying J, Xue W, Xie T, Tao L, and Zhu F (2020) Protein functional annotation of simultaneously improved stability, accuracy and false discovery rate achieved by a sequence-based deep learning. *Brief Bioinform* **21**:1437–1447.

Hu M, Patel SK, Zhou T, and Rohan LC (2015) Drug transporters in tissues and cells relevant to sexual transmission of HIV: implications for drug delivery. *J Control Release* **219**:681–696.

Kanehisa M, Sato Y, Furumichi M, Morishima K, and Tanabe M (2019) New approach for understanding genome variations in KEGG. *Nucleic Acids Res* **47** (D1):D590–D595.

Karimian M, Momeni A, Farmohammadi A, Behjati M, Jafari M, and Raygan F (2020) Common gene polymorphism in ATP-binding cassette transporter A1 and coronary artery disease: a genetic association study and a structural analysis. *J Cell Biochem* **121**:3345–3357.

Kawahara I, Nishikawa S, Yamamoto A, Kono Y, and Fujita T (2020) The impact of breast cancer resistance protein (BCRP/ABCG2) on drug transport across Caco-2 cell monolayers. *Drug Metab Dispos* **48**:491–498.

Kemp S, Pujol A, Waterham HR, van Geel BM, Boehm CD, Raymond GV, Cutting GR, Wanders RJ, and Moser HW (2001) ABCD1 mutations and the X-linked adrenoleukodystrophy mutation database: role in diagnosis and clinical correlations. *Hum Mutat* **18**:499–515.

Kosa RE, Lazzaro S, Bi YA, Tierney B, Gates D, Modi S, Costales C, Rodrigues AD, Tremaine LM, and Varma MV (2018) Simultaneous assessment of transporter-mediated drug-drug interactions using a probe drug cocktail in cynomolgus monkey. *Drug Metab Dispos* **46**:1179–1189.

Kounelis F, Kanterakis A, Kanavos A, Pandi MT, Kordou Z, Manusama O, Vonitsanos G, Katsila T, Tsermpini EE, Lauschke VM, et al. (2020) Documentation of clinically relevant genomic biomarker allele frequencies in the next-generation FINDbase worldwide database. *Hum Mutat* **41**:1112–1122.

Lane TS, Rempe CS, Davitt J, Staton ME, Peng Y, Soltis DE, Melkonian M, Deyholos M, Leebens-Mack JH, Chase M, et al. (2016) Diversity of ABC transporter genes across the plant kingdom and their potential utility in biotechnology. *BMC Biotechnol* **16**:47.

Lee CC, Huang PJ, Yeh YM, Chen SY, Chiu CH, Cheng WH, and Tang P (2019) Pathogenic protist transmembranome database (PPTdb): a web-based platform for searching and analysis of protist transmembrane proteins. *BMC Bioinformatics* **20** (Suppl 13):382.

Lewis SS and Girisha KM (2020) Whole exome sequencing identifies a novel pathogenic variation [p.(Gly194valfs*7)] in SLC45A2 in the homozygous state in multiple members of a family with oculocutaneous albinism in southern India. *Clin Exp Dermatol* **45**:409–413.

Li B, Tang J, Yang Q, Li S, Cui X, Li Y, Chen Y, Xue W, Li X, and Zhu F (2017) NOREVA: normalization and evaluation of MS-based metabolomics data. *Nucleic Acids Res* **45** (W1):W162–W170.

Li BB, Chen ZY, Jiang N, Guo S, Yang JQ, Chai SB, Yan HF, Sun PM, Hu G, Zhang T, et al. (2020a) Correction to: simulated microgravity significantly altered metabolism in epidermal stem cells. *In Vitro Cell Dev Biol Anim* **56**:493–494.

Li F, Zhou Y, Zhang X, Tang J, Yang Q, Zhang Y, Luo Y, Hu J, Xue W, Qiu Y, et al. (2020b) SSizer: determining the sample sufficiency for comparative biological study. *J Mol Biol* **432**:3411–3421.

Li XX, Yin J, Tang J, Li Y, Yang Q, Xiao Z, Zhang R, Wang Y, Hong J, Tao L, et al. (2018a) Determining the balance between drug efficacy and safety by the network and biological system profile of its therapeutic target. *Front Pharmacol* **9**:1245.

Li YH, Yu CY, Li XX, Zhang P, Tang J, Yang Q, Fu T, Zhang X, Cui X, Tu G, et al. (2018b) Therapeutic target database update 2018: enriched resource for facilitating bench-to-clinic research of targeted therapeutics. *Nucleic Acids Res* **46** (D1):D1121–D1127.

Lin L, Yee SW, Kim RB, and Giacomini KM (2015) SLC transporters as therapeutic targets: emerging opportunities. *Nat Rev Drug Discov* **14**:543–560.

Liu Y, Zheng X, Yu Q, Wang H, Tan F, Zhu Q, Yuan L, Jiang H, Yu L, and Zeng S (2016) Epigenetic activation of the drug transporter OCT2 sensitizes renal cell carcinoma to oxaliplatin. *Sci Transl Med* **8**:348ra97.

Lozano E, Macias RIR, Monte MJ, Asensio M, Del Carmen S, Sanchez-Vicente L, Alonso-Peña M, Al-Abdulla R, Munoz-Garrido P, Satriano L, et al. (2019) Causes of hOCT1-dependent cholangiocarcinoma resistance to sorafenib and sensitization by tumor-selective gene therapy. *Hepatology* **70**:1246–1261.

Mak L, Marcus D, Howlett A, Yarova G, Duchateau G, Klaffke W, Bender A, and Glen RC (2015) Metrabase: a cheminformatics and bioinformatics database for small molecule transporter data analysis and (Q)SAR modeling. *J Cheminform* **7**:31.

Mendez D, Gaulton A, Bento AP, Chambers J, De Veij M, Félix E, Magariños MP, Mosquera JF, Mutowo P, Nowotka M, et al. (2019) ChEMBL: towards direct deposition of bioassay data. *Nucleic Acids Res* **47** (D1):D930–D940.

Morrissey KM, Wen CC, Johns SJ, Zhang L, Huang SM, and Giacomini KM (2012) The UCSF-FDA TransPortal: a public drug transporter database. *Clin Pharmacol Ther* **92**:545–546.

Müller F, Sharma A, König J, and Fromm MF (2018) Biomarkers for in vivo assessment of transporter function. *Pharmacol Rev* **70**:246–277.

Newport TD, Sansom MSP, and Stansfeld PJ (2019) The MemProtMD database: a resource for membrane-embedded protein structures and their lipid interactions. *Nucleic Acids Res* **47** (D1):D390–D397.

Nie Y, Yang J, Liu S, Sun R, Chen H, Long N, Jiang R, and Gui C (2020) Genetic polymorphisms of human hepatic OATPs: functional consequences and effect on drug pharmacokinetics. *Xenobiotica* **50**:297–317.

Nigam SK (2015) What do drug transporters really do? *Nat Rev Drug Discov* **14**:29–44.

Nigam SK (2018) The SLC22 transporter family: a paradigm for the impact of drug transporters on metabolic pathways, signaling, and disease. *Annu Rev Pharmacol Toxicol* **58**:663–687.

Nixon M, Mackenzie SD, Taylor AI, Homer NZ, Livingstone DE, Mouras R, Morgan RA, Mole DJ, Stimson RH, Reynolds RM, et al. (2016) ABCC1 confers tissue-specific sensitivity to

cortisol versus corticosterone: A rationale for safer glucocorticoid replacement therapy. *Sci Transl Med* **8**:352ra109.
Papatheodorou I, Moreno P, Manning J, Fuentes AM, George N, Fexova S, Fonseca NA, Füllgrabe A, Green M, Huang N, et al. (2020) Expression atlas update: from tissues to single cells. *Nucleic Acids Res* **48** (D1):D77–D83.
Peng L and Zhong X (2015) Epigenetic regulation of drug metabolism and transport. *Acta Pharm Sin B* **5**:106–112.
Peng LL, Zhao YQ, Zhou ZY, Jin J, Zhao M, Chen XM, Chen LY, Cai YF, Li JL, and Huang M (2016) Associations of MDR1, TBXA2R, PLA2G7, and PEAR1 genetic polymorphisms with the platelet activity in Chinese ischemic stroke patients receiving aspirin therapy. *Acta Pharmacol Sin* **37**:1442–1448.
Peng X, Wilken SE, Lankiewicz TS, Gilmore SP, Brown JL, Henske JK, Swift CL, Salamov A, Barry K, Grigoriev IV, et al. (2021) Genomic and functional analyses of fungal and bacterial consortia that enable lignocellulose breakdown in goat gut microbiomes. *Nat Microbiol* **6**:499–511.
Penmatsa A, Wang KH, and Gouaux E (2013) X-ray structure of dopamine transporter elucidates antidepressant mechanism. *Nature* **503**:85–90.
Rodieux F, Gotta V, Pfister M, and van den Anker JN (2016) Causes and consequences of variability in drug transporter activity in pediatric drug therapy. *J Clin Pharmacol* **56** (Suppl 7):S173–S192.
Safar Z, Kis E, Erdo F, Zolnerciks JK, and Krajcsi P (2019) ABCG2/BCRP: variants, transporter interaction profile of substrates and inhibitors. *Expert Opin Drug Metab Toxicol* **15**:313–328.
Saier MH, Reddy VS, Moreno-Hagelsieb G, Hendargo KJ, Zhang Y, Iddamsetty V, Lam KJK, Tian N, Russum S, Wang J, et al. (2021) The transporter classification database (TCDB): 2021 update. *Nucleic Acids Res* **49** (D1):D461–D467.
Sakai M, Nagayasu K, Shibui N, Andoh C, Takayama K, Shirakawa H, and Kaneko S (2021) Prediction of pharmacological activities from chemical structures with graph convolutional neural networks. *Sci Rep* **11**:525.
Sakil HAM, Stantic M, Wolfsberger J, Brage SE, Hansson J, and Wilhelm MT (2017) ΔNp73 regulates the expression of the multidrug-resistance genes ABCB1 and ABCB5 in breast cancer and melanoma cells - a short report. *Cell Oncol (Dordr)* **40**:631–638.
Sarti E, Aleksandrova AA, Ganta SK, Yavatkar AS, and Forrest LR (2019) EncoMPASS: an online database for analyzing structure and symmetry in membrane proteins. *Nucleic Acids Res* **47** (D1):D315–D321.
Shen H, Lai Y, and Rodrigues AD (2017) Organic anion transporter 2: an enigmatic human solute carrier. *Drug Metab Dispos* **45**:228–236.
Sherry ST, Ward MH, Kholodov M, Baker J, Phan L, Smigielski EM, and Sirotkin K (2001) dbSNP: the NCBI database of genetic variation. *Nucleic Acids Res* **29**:308–311.
Shu R, Wang C, Meng Q, Liu Z, Wu J, Sun P, Sun H, Ma X, Huo X, and Liu K (2019) Resveratrol enhances the protective effects of JBP485 against indomethacin-induced rat intestinal damage in vivo and vitro through up-regulating oligopeptide transporter 1 (Pept1). *Biomed Pharmacother* **111**:251–261.
Sosnay PR, Castellani C, Corey M, Dorfman R, Zielenski J, Karchin R, Penland CM, and Cutting GR (2011) Evaluation of the disease liability of CFTR variants. *Methods Mol Biol* **742**:355–372.
Stopfer P, Giessmann T, Hohl K, Sharma A, Ishiguro N, Taub ME, Zimdahl-Gelling H, Gansser D, Wein M, Ebner T, et al. (2016) Pharmacokinetic evaluation of a drug transporter cocktail consisting of digoxin, furosemide, metformin, and rosuvastatin. *Clin Pharmacol Ther* **100**:259–267.
Tang J, Fu J, Wang Y, Li B, Li Y, Yang Q, Cui X, Hong J, Li X, Chen Y, et al. (2020) ANPELA: analysis and performance assessment of the label-free quantification workflow for metaproteomic studies. *Brief Bioinform* **21**:621–636.
Terada T, Noda S, and Inui K (2015) Management of dose variability and side effects for individualized cancer pharmacotherapy with tyrosine kinase inhibitors. *Pharmacol Ther* **152**:125–134.
To KKW, Wu X, Yin C, Chai S, Yao S, Kadioglu O, Efferth T, Ye Y, and Lin G (2017) Reversal of multidrug resistance by Marsdenia tenacissima and its main active ingredients polyoxypregnanes. *J Ethnopharmacol* **203**:110–119.
Tordai H, Jakab K, Gyimesi G, András K, Brózik A, Sarkadi B, and Hegedus T (2017) ABCMdb reloaded: updates on mutations in ATP binding cassette proteins. *Database (Oxford)* **2017**:bax023.
Tracewska AM, Kocyła-Karczmarewicz B, Rafalska A, Murawska J, Jakubaszko-Jablonska J, Rydzanicz M, Stawiński P, Ciara E, Khan MI, Henkes A, et al. (2019) Genetic spectrum of ABCA4-associated retinal degeneration in poland. *Genes (Basel)* **10**:959.
Trezza A, Bernini A, Langella A, Ascher DB, Pires DEV, Sodi A, Passerini I, Pelo E, Rizzo S, Niccolai N, et al. (2017) A computational approach from gene to structure analysis of the human ABCA4 transporter involved in genetic retinal diseases. *Invest Ophthalmol Vis Sci* **58**:5320–5328.
Uhlén M, Fagerberg L, Hallström BM, Lindskog C, Oksvold P, Mardinoglu A, Sivertsson Å, Kampf C, Sjöstedt E, Asplund A, et al. (2015) Proteomics. Tissue-based map of the human proteome. *Science* **347**:1260419.
UniProt Consortium (2021) UniProt: the universal protein knowledgebase in 2021. *Nucleic Acids Res* **49** (D1):D480–D489.
Veldic M, Millischer V, Port JD, Ho AM, Jia YF, Geske JR, Biernacka JM, Backlund L, McElroy SL, Bond DJ, et al. (2019) Genetic variant in SLC1A2 is associated with elevated anterior cingulate cortex glutamate and lifetime history of rapid cycling. *Transl Psychiatry* **9**:149.
Verkman AS, Synder D, Tradtrantip L, Thiagarajah JR, and Anderson MO (2013) CFTR inhibitors. *Curr Pharm Des* **19**:3529–3541.
Wang J, Yu L, Jiang H, Zheng X, and Zeng S (2020a) Epigenetic regulation of differentially expressed drug-metabolizing enzymes in cancer. *Drug Metab Dispos* **48**:759–768.
Wang X, Rai N, Merchel Piovesan Pereira B, Eetemadi A, and Tagkopoulos I (2020b) Accelerated knowledge discovery from omics data by optimal experimental design. *Nat Commun* **11**:5026.
Wang Y, Li F, Zhang Y, Zhou Y, Tan Y, Chen Y, and Zhu F (2020c) Databases for the targeted COVID-19 therapeutics. *Br J Pharmacol* **177**:4999–5001.
Wang Y, Zhang S, Li F, Zhou Y, Zhang Y, Wang Z, Zhang R, Zhu J, Ren Y, Tan Y, et al. (2020d) Therapeutic target database 2020: enriched resource for facilitating research and early development of targeted therapeutics. *Nucleic Acids Res* **48** (D1):D1031–D1041.
Wang Y, Zhu Q, Hu H, Zhu H, Yang B, He Q, Yu L, and Zeng S (2021) Upregulation of histone acetylation reverses organic anion transporter 2 repression and enhances 5-fluorouracil sensitivity in hepatocellular carcinoma. *Biochem Pharmacol* **188**:114546.
Wishart DS, Feunang YD, Guo AC, Lo EJ, Marcu A, Grant JR, Sajed T, Johnson D, Li C, Sayeeda Z, et al. (2018) DrugBank 5.0: a major update to the DrugBank database for 2018. *Nucleic Acids Res* **46** (D1):D1074–D1082.
Xue W, Wang P, Li B, Li Y, Xu X, Yang F, Yao X, Chen YZ, Xu F, and Zhu F (2016) Identification of the inhibitory mechanism of FDA approved selective serotonin reuptake inhibitors: an insight from molecular dynamics simulation study. *Phys Chem Chem Phys* **18**:3260–3271.
Yang H, Qin C, Li YH, Tao L, Zhou J, Yu CY, Xu F, Chen Z, Zhu F, and Chen YZ (2016) Therapeutic target database update 2016: enriched resource for bench to clinical drug target and targeted pathway information. *Nucleic Acids Res* **44** (D1):D1069–D1074.
Yang M, Ma J, Ruan J, Ye Y, Fu PP, and Lin G (2019) Intestinal and hepatic biotransformation of pyrrolizidine alkaloid N-oxides to toxic pyrrolizidine alkaloids. *Arch Toxicol* **93**:2197–2209.
Yang Q, Hong J, Li Y, Xue W, Li S, Yang H, and Zhu F (2020a) A novel bioinformatics approach to identify the consistently well-performing normalization strategy for current metabolomic studies. *Brief Bioinform* **21**:2142–2152.
Yang Q, Li B, Tang J, Cui X, Wang Y, Li X, Hu J, Chen Y, Xue W, Lou Y, et al. (2020b) Consistent gene signature of schizophrenia identified by a novel feature selection strategy from comprehensive sets of transcriptomic data. *Brief Bioinform* **21**:1058–1068.
Yang Q, Wang Y, Zhang Y, Li F, Xia W, Zhou Y, Qiu Y, Li H, and Zhu F (2020c) NOREVA: enhanced normalization and evaluation of time-course and multi-class metabolomic data. *Nucleic Acids Res* **48** (W1):W436–W448.
Ye C, Han K, Lei J, Zeng K, Zeng S, Ju H, and Yu L (2018) Inhibition of histone deacetylase 7 reverses concentrative nucleoside transporter 2 repression in colorectal cancer by up-regulating histone acetylation state. *Br J Pharmacol* **175**:4209–4217.
Ye J, Xu M, Tian X, Cai S, and Zeng S (2019) Research advances in the detection of miRNA. *J Pharm Anal* **9**:217–226.
Yee SW, Brackman DJ, Ennis EA, Sugiyama Y, Kamdem LK, Blanchard R, Galetin A, Zhang L, and Giacomini KM (2018) Influence of transporter polymorphisms on drug disposition and response: a perspective from the international transporter consortium. *Clin Pharmacol Ther* **104**:803–817.
Yin J, Li F, Zhou Y, Mou M, Lu Y, Chen K, Xue J, Luo Y, Fu J, He X, et al. (2021) INTEDE: interactome of drug-metabolizing enzymes. *Nucleic Acids Res* **49** (D1):D1233–D1243.
Yin J, Sun W, Li F, Hong J, Li X, Zhou Y, Lu Y, Liu M, Zhang X, Chen N, et al. (2020) VARIDT 1.0: variability of drug transporter database. *Nucleic Acids Res* **48** (D1):D1042–D1050.
Yu AM, Ingelman-Sundberg M, Cherrington NJ, Aleksunes LM, Zanger UM, Xie W, Jeong H, Morgan ET, Turnbaugh PJ, Klaassen CD, et al. (2017) Regulation of drug metabolism and toxicity by multiple factors of genetics, epigenetics, lncRNAs, gut microbiota, and diseases: a meeting report of the 21st International Symposium on Microsomes and Drug Oxidations (MDO). *Acta Pharm Sin B* **7**:241–248.
Yu AM, Jian C, Yu AH, and Tu MJ (2019) RNA therapy: Are we using the right molecules? *Pharmacol Ther* **196**:91–104.
Yu AM and Zhong XB (2016) Advanced knowledge in drug metabolism and pharmacokinetics. *Acta Pharm Sin B* **6**:361–362.
Yu L, Rodriguez RA, Chen LL, Chen LY, Perry G, McHardy SF, and Yeh CK (2016) 1,3-propanediol binds deep inside the channel to inhibit water permeation through aquaporins. *Protein Sci* **25**:433–441.
Yu S, Wu Y, Li C, Qu Z, Lou G, Guo X, Ji J, Li N, Guo M, Zhang M, et al. (2020) Comprehensive analysis of the SLC16A gene family in pancreatic cancer via integrated bioinformatics. *Sci Rep* **10**:7315.
Zhang Y and Hagenbuch B (2019) Protein-protein interactions of drug uptake transporters that are important for liver and kidney. *Biochem Pharmacol* **168**:384–391.
Zheng G, Yang F, Fu T, Tu G, Chen Y, Yao X, Xue W, and Zhu F (2018) Computational characterization of the selective inhibition of human norepinephrine and serotonin transporters by an escitalopram scaffold. *Phys Chem Chem Phys* **20**:29513–29527.
Zhou S, Zeng S, and Shu Y (2021) Drug-drug interactions at organic cation transporter 1. *Front Pharmacol* **12**:628705.
Zhou Y, Ye C, Lou Y, Liu J, Ye S, Chen L, Lei J, Guo S, Zeng S, and Yu L (2020) Epigenetic mechanisms underlying organic solute transporter beta repression in colorectal cancer. *Mol Pharmacol* **97**:259–266.
Zhu Q, Yu L, Qin Z, Chen L, Hu H, Zheng X, and Zeng S (2019) Regulation of *OCT2* transcriptional repression by histone acetylation in renal cell carcinoma. *Epigenetics* **14**:791–803.

Address correspondence to: Dr. Su Zeng, College of Pharmaceutical Sciences, Zhejiang University, Hangzhou, China. E-mail: zengsu@zju.edu.cn; or Dr. Feng Zhu, College of Pharmaceutical Sciences, Zhejiang University, Hangzhou, China. E-mail: zhufeng@zju.edu.cn