Transporter Database, TP-Search: A Web-Accessible Comprehensive Database for Research in Pharmacokinetics of Drugs

This Letter to the Editor informs the readers of TP-Search, a unique comprehensive database for membrane transporter proteins that we have constructed to facilitate the study of drug transporters on a broad scale in the world and to provide a research tool for optimization of pharmacokinetic properties in terms of transporters during the early stage of drug development in pharmaceutical companies.

During the past decade, there has been a significant increase in the molecular characterization of transporter proteins in animals and humans (1). With newer information on the genetic/genomic studies, this has led to a better understanding of the importance of such transporter proteins as one of the main determinant factors to play a key role in drug disposition; that is, absorption, distribution, and excretion (ADE) of drugs (2–4). Because the amount of available data is rapidly increasing, a need for a publicly accessible database with comprehensive information about all of the known membrane transporters becomes increasingly important.

We have constructed TP-Search, a Web-accessible relational database on ADE-associated transporter proteins (http://www.tp-search.jp/), enabling users to search dynamically transporter-related information by chemical structures/names of substrate/inhibitor/inducers, gene expression, functions, drug-drug interaction involving transporters, and so on.

The other databases on transporters, which are currently available, are http://nutrigen.4t.com/humanabc.htm (database on ABC transporters by M. Müller), http://www.med.rug.nl/mdl/ (database of University Hospital Groningen), http://www.gene.ucl.ac.uk/nomenclature/genefamily/abc.html (HGNC gene family nomenclature ABC transporters), http://lab.digibench.net/transporter/ (human membrane transporter database), http://xin.cz3.nus.edu.sg/group/adment/adment.asp (ADME-associated proteins database), and http://www.mhc.com/PGP/index.html (P-glycoprotein interaction). These have appeared to provide only certain aspects of specific class or group of membrane transporter proteins, whereas TP-Search aims at providing a comprehensive database on drug-transporters. Among those databases, the human membrane transporter database has been intended to support pharmacogenomic studies and so provides much information on sequence variants, altered functions caused by polymorphisms/mutations, and (patho)physiological role and associated diseases (5). The ADME-associated protein database provides comprehensive information on ADME-associated proteins, which include not only membrane transporter proteins involved in drug disposition, but also other proteins, such as plasma proteins, intracellular binding proteins, and drug metabolizing enzymes (6). Other transporter databases listed above are mainly focused on the information for ABC-transporters.

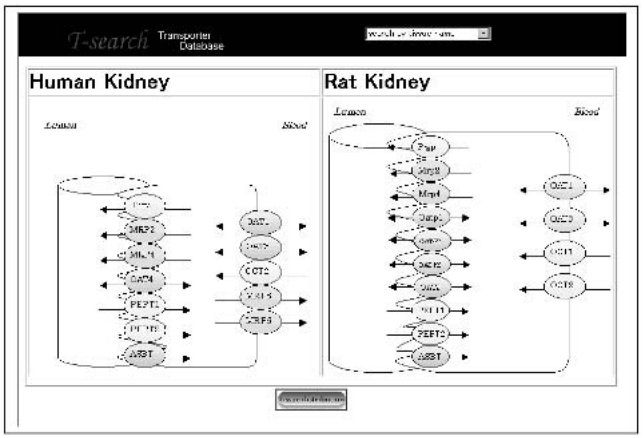

Fig. 1. Example of search results on transporters expressed in human and rat kidney.

Our methodology was as follows. Membrane transporter proteins were selected from a comprehensive search of available literature consisting of research papers, review articles, pharmacology textbooks, and other relevant publications (via PubMed; http://www.ncbi.nlm.gov/PubMed/), resulting in approximately 1,940 articles published from 1968 to 2002. The system is a typical Web application built on Application server, Web server, and Relational Database Management System (RDMS) to provide the services via the Internet. The user connects with the URL at http://www.tp-search.jp/ by a Web browser such as Netscape Navigator or Microsoft Internet Explorer.

The database, TP-Search, contains information on more than 75 membrane transporters (Table I), including cDNA and amino acid sequences, gene family, putative membrane topology, driving force, transport direction, substrate/inhibitor/inducer (chemical structures and kinetic data, i.e., Km/Ki), and tissue distribution in humans as well as in mice and rats, and drug-drug interactions involving transporters. All information available in this database is linked to the original references in PubMed, which ensures the users can confirm the validity of data and to obtain more detailed information available in the original references.

Terminology regarding genes often causes confusion. In our database, we use primarily the "Nomenclature of Mammalian Transporter Genes," (http://www.gene.ucl.ac.uk/cgi-bin/nomenclature/searchgenes.pl/), such as the solute carrier superfamily (SLC) and ATP-binding cassette transporters (ABC). These standardized gene names, accompanied by conventional names, are both given in this database. The sequential information for transporters posted in the database was available through "Locus-Link" (http://www.ncbi.nlm.nih.gov/LocusLink/), and names and structures of the compounds, such as substrates/inhibitors/inducers, were searched through "Chem-Link" and "Japanese Accepted Names for Pharmaceuticals" (http://moldb.nihs.go.jp/jan/).

TP-Search is searchable by transporter name, tissue name (liver, kidney, intestine, brain, and expression in cell line; Fig. 1), substrate/inhibitor/inducer name, and drug-drug interaction. Implemented as a relational database, searches involving any combination of these options or selection field are also supported.

Because drug transporters have demonstrated a broad substrate specificity, drug-drug interaction involving these transporters is considered very likely. Approximately 1,200

0724-8741/04/1100-2133/0

Table I. Membrane Transporters Archived in TP-Search

Transporters	Human	Mouse	Rat
P-glycoprotein (MDR)	MDR1	Mdr1a, Mdr1b	Mdr1a, Mdr1b
Multidrug resistance–associated protein	MRP1, MRP2, MRP3, MRP4, MRP5, MRP6	Mrp1, Mrp2, Mrp5	Mrp1, Mrp2, Mrp3, Mrp6
Breast cancer resistant protein	BCRP	Bcrp	Bcrp
Bile salt export pump	BSEP	Bsep	Bsep
Organic anion transporting polypeptide	OATP-A, OATP-B, OATP-C, OATP-D, OATP-E, OATP-8, PGT	Oatp1, Oatp2, Oatp4, Oatp5, Pgt	Oatp1, Oatp2, Oatp3, Oatp4, OAT-K1, OAT-K2, Pgt
Bile acid transporter	NTCP, ASBT	Ntcp, Asbt	Ntcp, Asbt
Organic anion transporter	OAT1, OAT2, OAT3, OAT4	OAT1, OAT2, OAT3	OAT1, OAT2, OAT3
Organic cation transporter	OCT1, OCT2, OCT3	OCT1, OCT2, OCT3	OCT1, OCT2, OCT3
Organic cation/carnitine transporter	OCTN1, OCTN2	OCTN1, OCTN2, OCTN3	OCTN1, OCTN2
Peptide transporter	PEPT1, PEPT2	PEPT1, PEPT2	PEPT1, PEPT2

compounds known as substrates/inhibitors/inducers, including their names and structures, are currently archived in this database. With respect to the information currently available in this database, the exact role of transporter proteins in the observed *in vivo* drug-drug interaction has not always been clearly defined. It might be just extrapolated from *in vitro* information, such as substrate affinity, inhibitory effect, and so forth. In addition, because the substrate specificity of CYP3A and P-glycoprotein overlaps, many drugs may be a substrate of both (7,8). In such cases, it is difficult to distinguish the contribution to the increased oral bioavailability between CYP3A and P-glycoprotein. When the role of transporter proteins in the *in vivo* drug-drug interaction was suggested or indicated in peer-reviewed references, such information was incorporated into this database, even though there might be the limitation of scientific validity of such data.

This database will be updated periodically (bimonthly or quarterly), so that information regarding newly identified ADE-associated membrane transport proteins and additional knowledge about function or related proteins will be added. Toward that end, a data submission interface will be available in the database.

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Received November 30, 2003; accepted July 23, 2004

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