

Knowledge management for transmembrane transporters

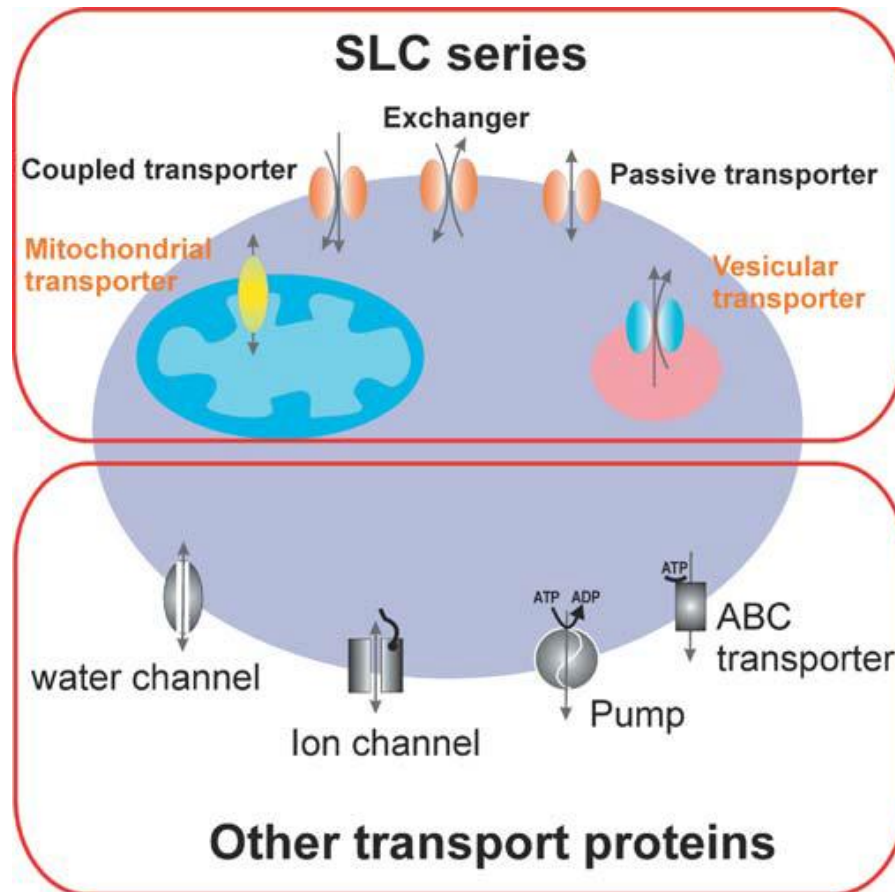
Tissue Knowledge Management Workshop

30th October 2013

Daniela Digles

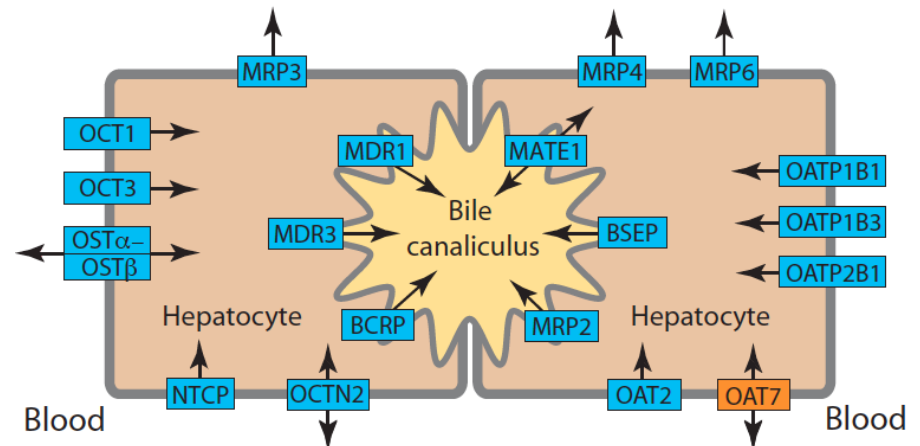


Transmembrane transporters



Membrane barriers

- Pharmacokinetic-relevant membrane barriers:
 - » Intestinal Drug Absorption
 - » Liver
 - » Kidney
 - » Blood-Brain Barrier



<http://bts.ucsf.edu/fdatransportal/organs/liver/>

Transporter databases - TCDB

- Transporter Classification Database
- Comprehensive classification system for membrane transport proteins (TC system)
- Descriptions, TC numbers, and examples for over 600 families
- Operated by the Saier Lab Bioinformatics Group (UCSD)
- Available at <http://www.tcdb.org/>
- References: Saier et al. *Nucl. Acids Res.* (2006) 34: D181-6
Saier et al. *Nucl. Acids Res.* (2009) 37: D274-8

Transporter databases – SLC Tables

- Solute Carrier (SLC) information
- Includes type of transport (Cotransporter, Exchanger, or Facilitated Transp.)
- Textual information on Substrates and Tissue and cellular expression
- Established by Hediger lab (University of Bern)
- Available at <http://www.bioparadigms.org/slc/intro.htm>
- References: reviews for each of the families

[–] SLC21 Organic anion transporter family

References

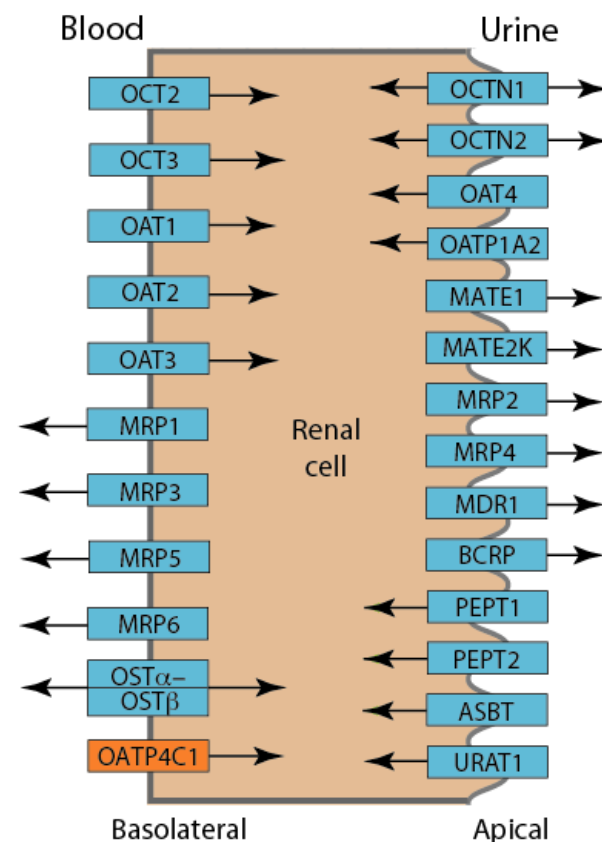
Original version of the SLC table:

Hagenbuch B, Stieger B. The SLC0 (former SLC21) superfamily of transporters. *Mol Aspects Med.* 2013 Apr;34(2-3):396-412.

Gene name	Protein name	Aliases	Transport type*	Substrates	Tissue and cellular expression
SLC01A2	OATP1A2			bile salts, organic anions and cations	brain (endothelial cells), kidney, intestine, liver (cholangiocytes), eye (ciliary body)
SLC01B1	OATP1B1			bile salts, organic anions	liver (hepatocytes)

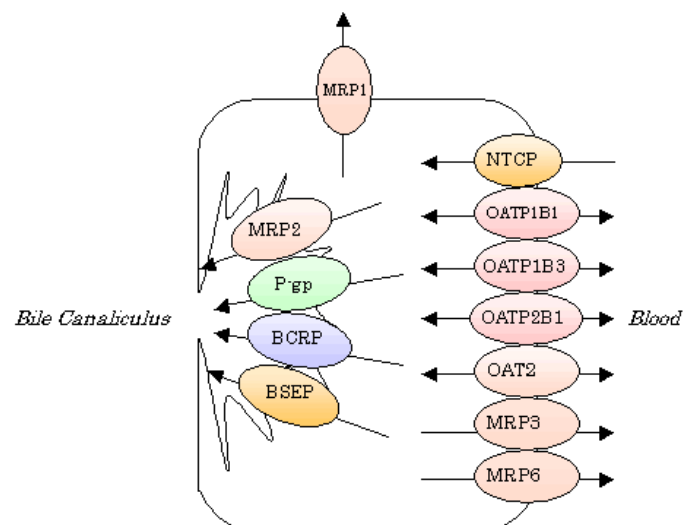
Transporter databases – UCSF-FDA TransPortal

- Repository of information on transporters important in the drug discovery process.
- Includes transporter expression, localization, substrates, inhibitors, and drug-drug interactions.
- Information on currently 32 transporters.
- Developed by Giacomini Lab (UCSF) supported by the Critical Paths Initiative of the FDA.
- Available at <http://bts.ucsf.edu/fdatransportal/>
- Reference: Morrissey et al. *Clin. Pharmacol. Ther.* (2012) 92(5):545-6



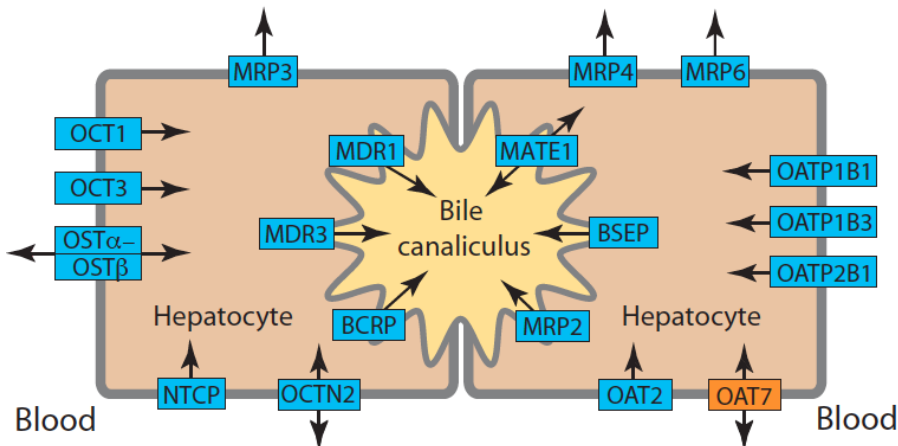
Transporter databases – TP-Search

- Database on transporters which play an important role in the pharmacokinetics of drugs.
- Information is extracted from a large number of published papers
- Bioactivity data (substrates, inhibitors, and inducers)
- Some information on tissue distribution (pictures and textual description of localization)
- Available at <http://www.tp-search.jp>
- Last update: June 2007

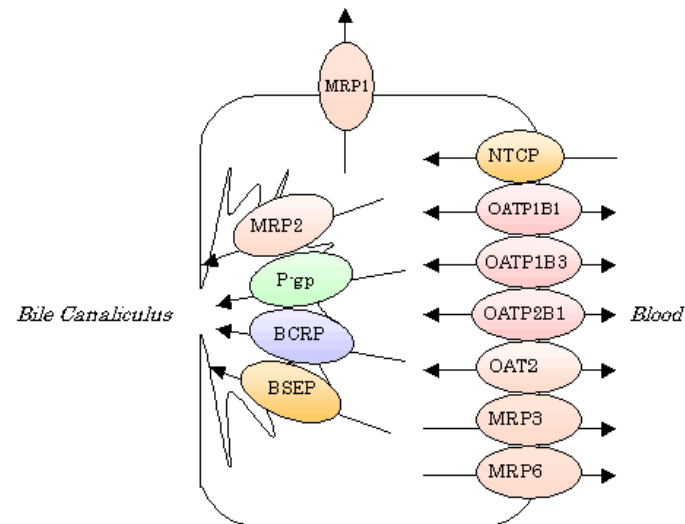


Tissue distribution of transporters

- Knowing the tissue expression is not enough!
- Which cells express the transporter and what influences expression levels?
- Where is the transporter located (eg. apical vs. basolateral)?
- Is the substrate transported out of or into the cell?



<http://bts.ucsf.edu/fdatransportal/organs/liver/>



<http://www.tp-search.jp>

Directionality of transport - resources

- apical/basolateral:
 - » GO (cellular component):
 - apical plasma membrane (GO:0016324)
 - basolateral plasma membrane (GO:0016323)
 - » Uniprot (Subcellular location annotation)
- in/out:
 - » Uniprot, TCDB (not available for every transporter)
Example: solute (out) + Na⁺ (out) → solute (in) + Na⁺ (in)
 - » Pathway databases (e.g. Reactome, Wikipathways...)

Example Hexose transport

CARBOHYDRATE DIGESTION

In intestinal lumen

starch → limit dextrins + maltose

at enterocyte surface





lactose → glucose + galactose

trehalose → glucose

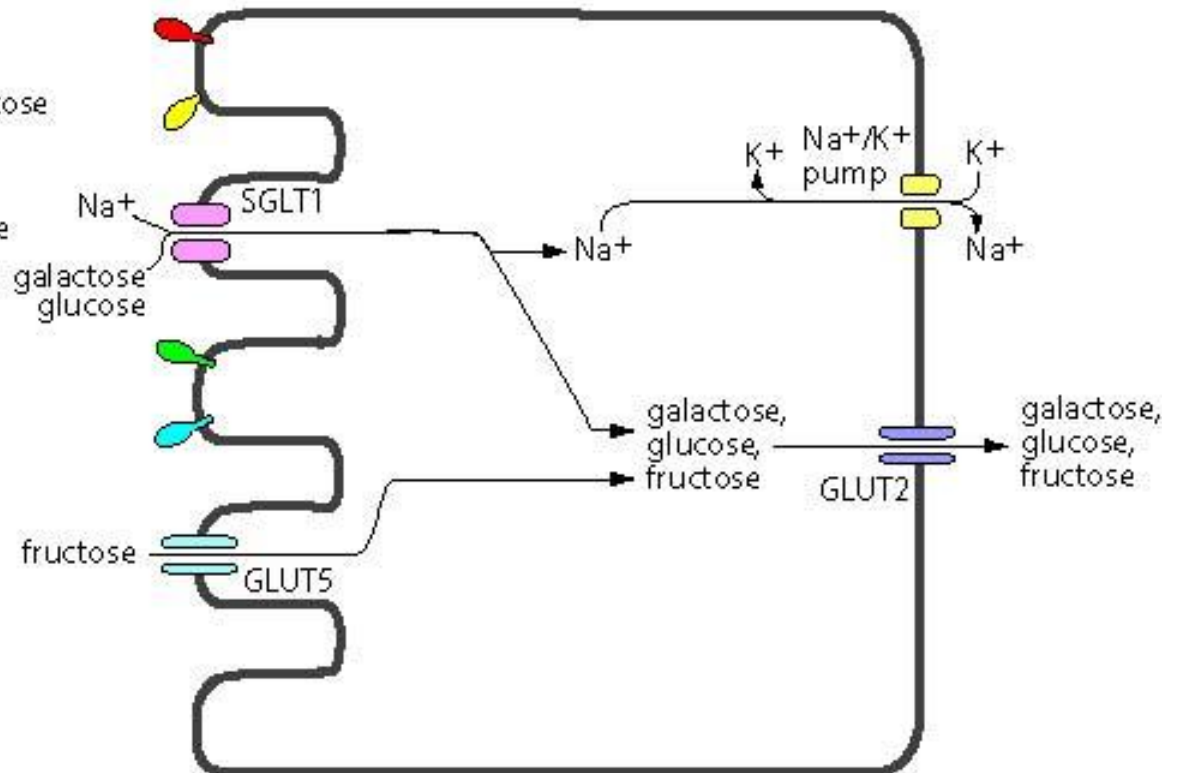
maltose → glucose

limit dextrins → glucose

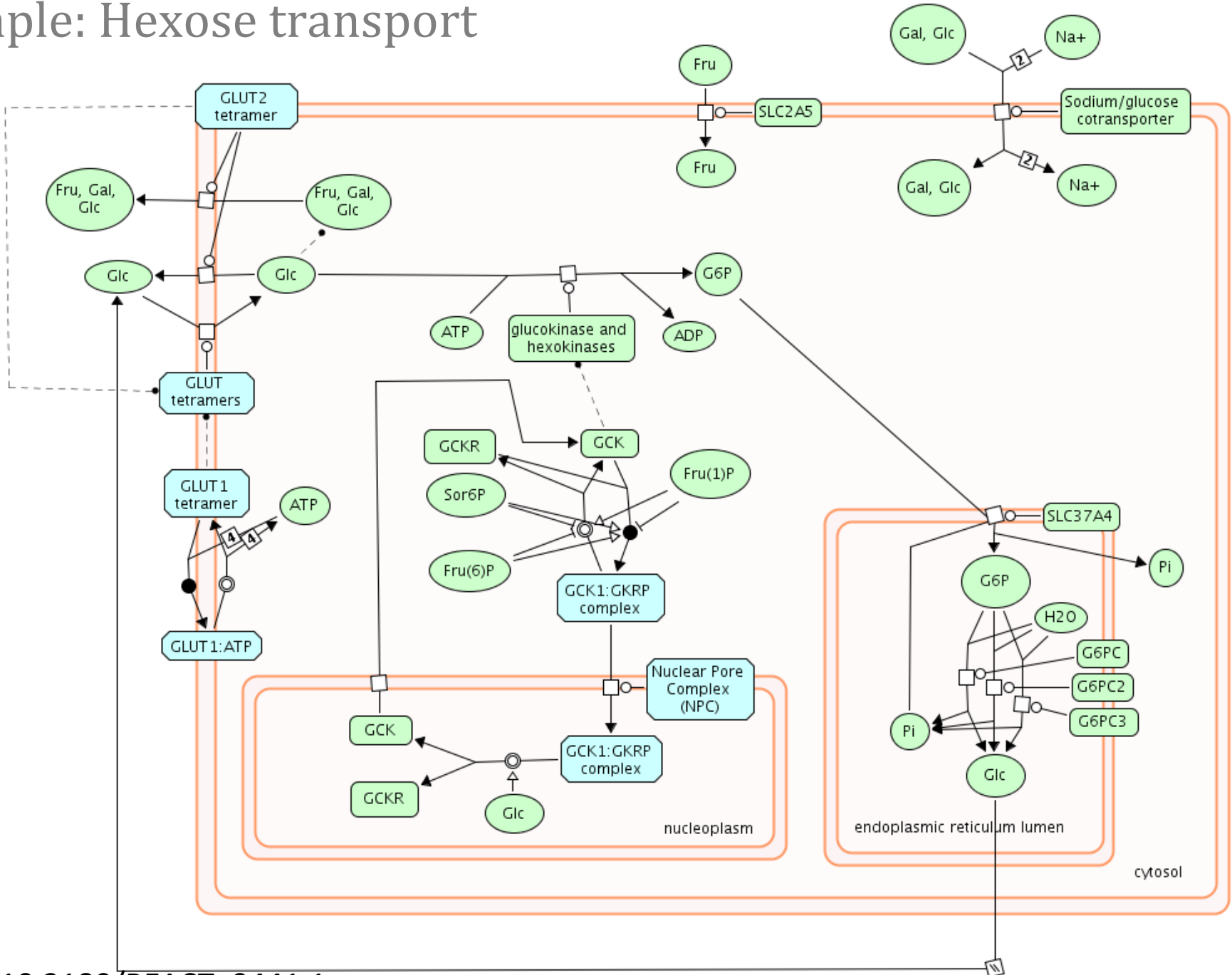
sucrose → glucose + fructose

-  lactase
-  trehalase
-  maltase-glucoamylase
-  sucrase-isomaltase

HEXOSE UPTAKE



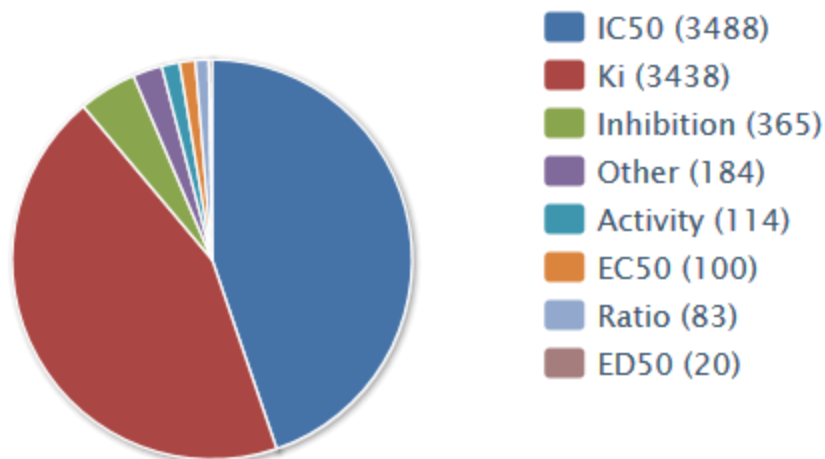
Example: Hexose transport



Transporter bioactivity data

- ChEMBL (<https://www.ebi.ac.uk/chembl/>)
 - » bioactivities for > 160 transporters and > 480 ion channels
 - » includes > 6.000 activities from TP-Search. Substrate/Inhibitor + or – shown in activity comment field
 - » Largest number of bioactivities for the human serotonin transporter

ChEMBL Activity Types for Target CHEMBL228

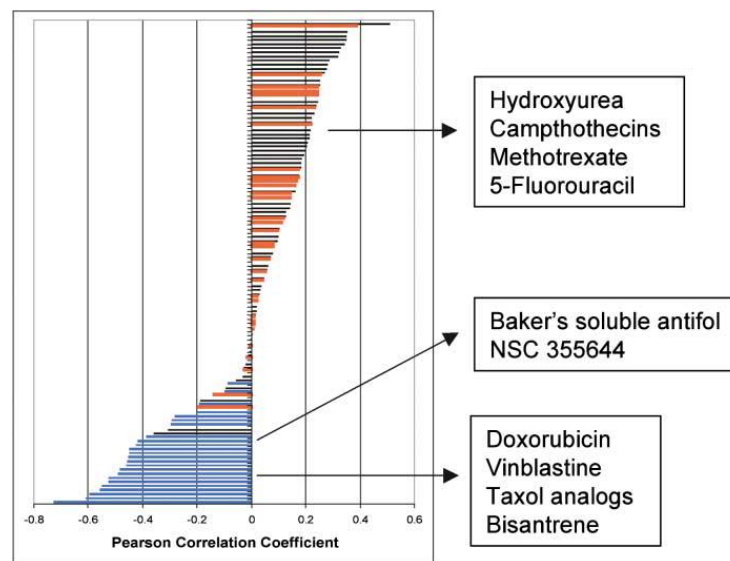


Total: 7798

Transporter bioactivity data

- „Gottesman dataset“
 - » Measured expression levels of ABC transporters in NCI-60 cell lines
 - » Calculated Pearson correlation coefficients of transporter expression and GI50 values of ~1400 compounds for 60 cancer cell lines
 - » Negative correlation for known substrates (blue)

- » Reference: Szakács et al.,
Cancer Cell (2004), 6, 129-137



Transporter classifications

- Aim: Incorporation of Pharmacology by Classification into the Open PHACTS system.
- Implemented: Enzyme Classification (EC), Gene Ontology (GO), and ChEMBL target classification

2 main possibilities:

- Transporter classification (TC): 5 level classification
 - » Detailed classification (large number of bacterial transporter families)
 - » Often the name of level 4 or 5 is missing
- IUPHAR/BPS (<http://www.guidetopharmacology.org/GRAC>)

Collection of transporters for the classification

- Uniprot (1078):
 - » organism:“Homo sapiens [9606]“ AND keyword:“Transport [KW-0813]“ and reviewed:yes
 - » manual exclusion of proteins (e.g. hemoglobine, apolipoproteins, ...)
- HGNC (954): selected gene families (e.g. ABC, SLC, ...)
- TCDB (804): only Homo sapiens
- ChEMBL (492): 136 transporter + 356 channels (all organisms)
- GO(40): Homo sapiens, GO:0022857 transmembrane transport activity, included in Swissprot, not found by any other source, manual exclusion

- 1444 membrane transport proteins (human + other organisms in ChEMBL)
- 1144 human membrane transport proteins
- 606 are in ChEMBL

Adaptations to TCDB classification

- Inclusion of missing transporters into TCDB
 - » BLAST against TCDB
 - » Comparison with other classification schemes
- no adaptations to the first 3 levels
- Level 4 (phylogenetic subfamily):
no adaptation, named unnamed subfamily or left out subfamily
- Level 5 (corresponds to substrate):
mostly left out (if redundant to subfamily), or named unnamed family

Acknowledgements

- University of Vienna (Pharmacoinformatics research group)
 - » Gerhard F. Ecker
 - » Michael Viereck
- Open PHACTS
 - » Christine Chichester
 - » Jean-Marc Neefs
- ChEMBL
 - » Anna Gaulton
- Funding: Open PHACTS, SFB35

