



The promiscuous binding of pharmaceutical drugs and their transporter-mediated uptake into cells: what we (need to) know and how we can do so

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A recent paper in this journal sought to counter evidence for the role of transport proteins in affecting drug uptake into cells, and questions that transporters can recognize drug molecules in addition to their endogenous substrates. However, there is abundant evidence that both drugs and proteins are highly promiscuous. Most proteins bind to many drugs and most drugs bind to multiple proteins (on average more than six), including transporters (mutations in these can determine resistance); most drugs are known to recognise at least one transporter. In this response, we alert readers to the relevant evidence that exists or is required. This needs to be acquired in cells that contain the relevant proteins, and we highlight an experimental system for simultaneous genome-wide assessment of carrier-mediated uptake in a eukaryotic cell (yeast).

Introduction

As part of a continuing discussion [1–6], Di and colleagues [7] recently published a paper in this journal in which they sought to counter the rather voluminous (and increasing) evidence for the proteinaceous carrier-mediated cellular uptake of pharmaceutical and other drugs (by genetically identified carriers being the norm) in favour of passive diffusion through the putative protein-free bilayer portions of biological membranes.

Di *et al.* [7] sought to dismiss a set of 38 articles that we mentioned [5] in favour of transporter-mediated drug uptake and referred to them as ‘opinion pieces and not research articles’. These 38 were of course chosen on the basis that they represented review articles that summarised many hundreds of research articles. Moreover, our own first survey [1] had more than 300 references alone (a restricted subset [8–10]). There is burgeoning evidence for the carrier-mediated view of drug uptake, and such reviews continue to appear [11–102].

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Douglas Kell took anMA (biochemistry) and DPhil (Oxon) in 1978. After several personal fellowships and other posts in what is now the University of Aberystwyth, he was awarded a Personal Chair (1992). He was a Founding Director of Aber Instruments Ltd (Queen's Award for Export Achievement, 1998). He moved to Manchester in 2002 and from 2005 to 2008 was Director, BBSRC Manchester Centre for Integrative Systems Biology (www.mcisb.org). Awards include the Fleming Award of the Society for General Microbiology (1986), RSC Interdisciplinary Science Award (2004), the FEBS-IUBMB Theodor Buecher prize, Royal Society/Wolfson Merit Award RSC Award in Chemical Biology (all 2005), and the 2006 Royal Society of Chemistry/Society of Analytical Chemistry Gold Medal. Since 2008 he has been serving on secondment as Chief Executive, UK Biotechnology and Biological Science Research Council.



Paul Dobson holds a degree in biochemistry and a PhD (2005) in structural biology with machine learning from UMIST. Following short postdoctoral positions in text mining and Raman spectroscopy, in 2006 he joined the group of Professor Douglas Kell at The University of Manchester, where he led cheminformatics research on mechanisms of drug uptake into cells, and yeast systems biology. He moved to Sheffield in 2010 as a CHELSI postdoctoral researcher with Dr Stephen Wilkinson, and in 2012 was appointed to a lectureship in biomanufacturing. His current research applies computer modelling to improve cell factories for the production of high-value chemicals and biotherapeutics.



Elizabeth (Bessie) Bilsland was born and brought up in Brazil where she graduated in agronomic engineering (ESALQ – USP), mastering in animal science and biotechnology. She obtained her PhD in Prof. Sunnerhagen's laboratory (Goteborg University – Sweden) working on yeast stress responses. She has over a decade of laboratory experience with the yeast *Saccharomyces cerevisiae* and is particularly interested in synthetic biology and assay development for yeast-based drug screens. She has supervised highly successful undergraduate and postgraduate students during both her PhD and post-doctoral work (Cambridge, UK). Recently, she established contacts with FAPESP and the British Consulate in Sao Paulo, which led to the organization of the Workshop on Synthetic Biology and Robotics, and to collaborations with laboratories from the University of Sao Paulo (USP) and Unicamp. She successfully combines a scientific career with raising three children.



Stephen Oliver is Professor of Systems Biology & Biochemistry and Director of the Centre for Systems Biology at Cambridge. He led the team that sequenced the first chromosome, from any organism, yeast chromosome III. His current work employs comprehensive, high-throughput analytical techniques – transcriptomics, proteomics, metabolomics, and rapid phenotyping. He is a member of EMBO, and a Fellow of the American Association for the Advancement of Science, American Academy of Microbiology, and Academy of Medical Sciences. Prof. Oliver was Kathleen Barton-Wright Memorial Lecturer of the Society for General Microbiology in 1996, and won the Biochemical Society's AstraZeneca Award in 2001.



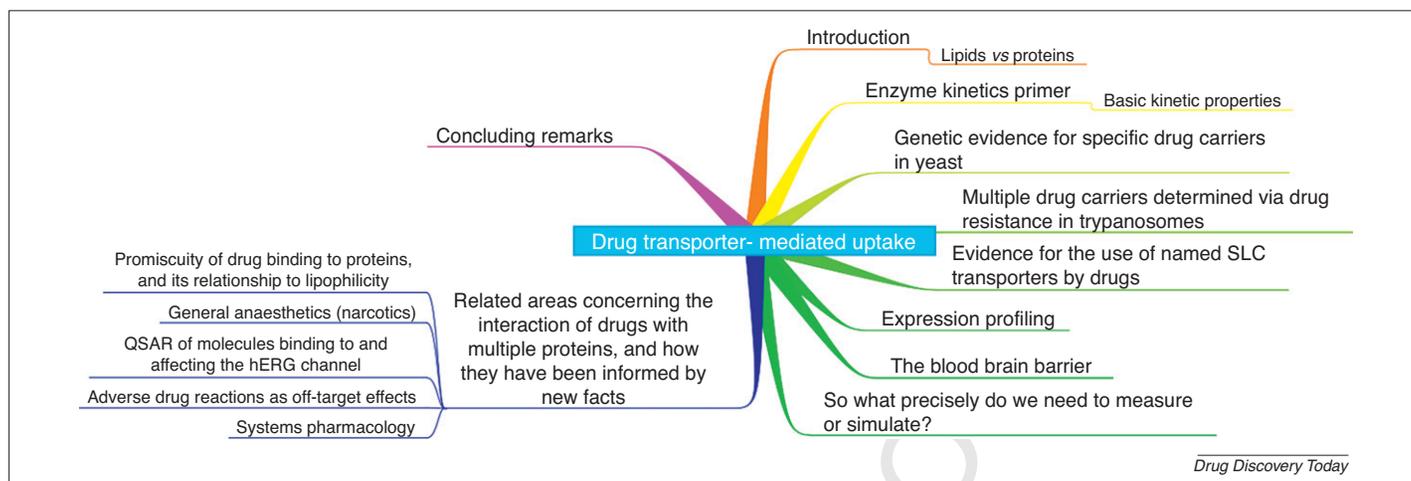


FIGURE 1

A 'mind map' [519] of the contents of this article.

Here, we seek to set down the kinds of experiments that might usefully be done (or indeed have already been done) and that would provide evidence for the overwhelming importance of drug and xenobiotic carriers in real biological membranes. Specifically, in studying transport into and out of cells it is sensible to study living cells rather than artificial membranes. The study of black lipid membranes or any other artificial constructs that are not themselves biological membranes (and thus lack carriers or other proteins) tells us nothing significant about the properties of real biological membranes that possess such carriers, and that is where our *in vivo* interest lies. We lay particular stress on the evidence that proteins and drugs are rather promiscuous with regard to their interactions with each other, because this lies at the heart of the interactions of drugs with multiple carriers. Moreover, we would remind readers of our previous stricture [5], epistemologically based [103], that absence of evidence is not evidence of absence. A 'mind map' summarising this article is shown in Fig. 1.

Lipids versus proteins

As rehearsed previously [5], there is little evidence that specific lipid moieties of the kinds typically found in eukaryotic membranes have substantially different biophysical properties from each other, and thus we assume that any transfer of xenobiotics across biomembranes that is claimed to go via lipid bilayers is similarly constrained. A factor of at most two in the variation of any flux for this seems reasonable. However, because carrier-mediated uptake requires the presence of genetically encoded proteins (any of which may be subject to post-translational modification) our focus is going to be on the evidence that named proteins with identified genetic loci have marked, reasonable and testable (or, indeed, tested) influences on the rate of transport of xenobiotics (and intermediary metabolites) across biological membranes. We shall also seek to avoid making claims not based simply on these facts. Many molecules have negligible permeability in artificial membrane assays, but much greater ones in biological cells; one of many examples is from a recent study [104] of cyclic peptides whose artificial membrane permeability, despite substantial lipophilicity, is both largely negligible and very poorly correlated with lipophilicity.

We also ignore discussions of artificial membranes lacking proteins. Whether biological membranes have protein:lipid ratios of 3:1, 1:1 or 2:3 is not of itself the issue, because one thing is certain [105]: the value is not 0:1. Also it is effectively the area ratio that governs the appearance of a membrane to a substrate as seen from the outside; the molar ratio of proteins to lipids [7] is a poor guide because lipids are so much smaller than proteins, although we certainly recognise the role of lipids in the barrier function of membranes. In addition, we note the rather elastic analysis by which a hexadecane layer either helps or hinders the passage of drugs through aqueous pores (cf. Figs 1 and 2 of Di *et al.* [7]). We note further that a membrane arrangement containing a hexadecane layer of unstated thickness is not really an adequate model for a phospholipid bilayer, if only because hexadecane (unlike pure phospholipid bilayer membranes, and even erythrocyte ghosts [106]) almost certainly does not admit transient aqueous pores. Equally, Di and colleagues [7] cite a remarkable paper [107] in which the correlation between rat brain permeability and the octanol–water partition coefficient is made reasonable solely by excluding the least convenient five of the 27 compounds measured. Finally, in contrast to the view of Di and colleagues [7], cellular membranes and lipid bilayers retain a high capacitance at frequencies low relative to their inverse charging time even when their conductance is quite substantial [108–112]. However, it is worth pointing to evidence that well-made bilayers have a background permeability to ions that is negligible, a fact exploited in nanopore-based methods of nucleic acid sequencing [113,114].

It is also worth stressing that if biological membranes were permeable to all kinds of solutes (whether via the bilayer portion of membranes or otherwise) they would not display osmotic properties at all. Because it is well known that they do so, it is clear that the non-carrier-mediated permeability of biological membranes to most solutes is, in fact, negligible. Recent evidence indicates that even the passage of extremely small molecules, such as water [115], glycerol [116–121], urea [122–125], hydroxyurea [126], ammonia/ammonium [127–132], bicarbonate [133–135], and CO₂ [136–138] across real biomembrane requires (or at least uses) protein transporters.

Finally, it is worth pointing out that (i) efflux pumps are well known for removing drugs from cells, which rather begs the question of why influx carriers did not accumulate them in the first place, and (ii) given that proteins (and not lipids) are normally the targets of pharmaceutical drugs, one might reasonably recognise that drugs can then be bound to and be transported by proteins, a fact for which there is a huge amount of evidence alluded to in the '38 reviews' and elsewhere above. Extensive other evidence for the promiscuous binding of drugs to multiple proteins, including transporters, is given below.

Evidence from enzyme kinetics

We will now rehearse the most relevant issues on drug transport that derive [139–141] from basic enzyme kinetics.

- (i) Rates of reactions of enzyme catalysts, including those of transporters, are (and are to be determined as) a function of at least the concentration of the enzyme catalyst molecules in question (linear over a wide range), the concentrations of substrates and products and inhibitors (usually nonlinear and interacting with each other in a manner accurately described by well-established equations). Unless one knows which enzymes are in a membrane, and their properties, one cannot say anything about their contribution to catalytic or transport activity, but neither can one ignore it when one knows which proteins are present.
- (ii) The rate of reaction of an enzyme is pH-dependent both because of the effects of pH on the enzyme and (if protonatable in the relevant pH range) of the substrate.
- (iii) The assumed degree of substrate specificity of any individual or (membrane-colocated) set of enzymes tells one 'precisely nothing' about either the actual specificities or the mechanisms of enzyme-mediated transport (including about diffusion), in that some enzymes are comparatively specific while many are exceedingly catholic (nonspecific) with respect to their substrate choice [142–146]. Well-known examples of substrate non-specificity in the world of pharmaceutical drugs and xenobiotics include the drug-metabolising enzymes cytochromes P450 [147–150] and carboxylesterase 1 [151], influx transporters such as the organic anion [152,153] and cation [154–157] SLC transporters, and efflux pumps such as the Multidrug And Toxin Extrusion (MATE) proteins [16,60,69,158–160] and P-glycoprotein [144,161–164] (and with promiscuous efflux transporters also being important in antiparasitic [165–167] and bacterial antibiotic resistance [168–177] and pharmacokinetics [88]). Many of these have exceptionally wide substrate specificities.
- (iv) 'Saturability' (or the lack of it) should not be used to exclude the involvement of a transporter protein if it is not known what kinds of multiple and parallel reactions are present, especially using multiple proteins [178]. The comment [7] 'the high local concentrations in the gut after oral dosing of drugs will saturate active drug transporters' has no meaning in the absence of knowledge of drug concentrations and transporter $K_{m,app}$ values (that are often mM). Note that even in real (as opposed to ideal and infinitely dilute) solutions, the diffusion coefficient is a function of substrate concentration because there is always a back reaction. Similarly, for an individual enzyme obeying typical reversible Briggs–Haldane

or Henri–Michaelis–Menten (HMM) kinetics, reactions may have substrate concentration-dependent kinetics indistinguishable from diffusion as (i) the rate of reaction versus substrate concentration can be linear over a wide range that is simply reflected in the apparent K_m ; (ii) after what may be a very short time in an initial velocity measurement, the back reaction may become very significant [and this is governed by the thermodynamics of all the coupled reactions, including those reflected in the Haldane relation (see below)].

- (v) The direction of transport of a substrate is governed by thermodynamics, and all transporters, such as enzyme catalysts, can transfer substrates in both directions across a membrane. The equilibrium constant K_{eq} for the overall reaction of a Michaelis–Menten enzyme is related to the forward and reverse Michaelis constants and maximal velocities according to the Haldane relation: $K_{eq} = (V_{m,f}K_{m,r})/(V_{m,r}K_{m,f})$ [179,180]. Beyond this there is no intrinsic 'polarity' of an enzyme or set of enzymes.
- (vi) Consequently, to establish the contributions of the various transporters to affecting the flux of drugs across particular membranes, we need to know two things in particular: (i) the concentrations of those transporters in the relevant membranes, (ii) something about the kinetics of each of them, such as their maximal turnover numbers and the concentrations of substrates and inhibitors that modify those rates, for example, by 50% (K_s , K_m and K_i values).

We next look at some of the carriers that have been identified experimentally using a parallel analysis of 'all' enzymes, that we have developed in baker's yeast (*Saccharomyces cerevisiae*).

Genetic evidence for specific drug carriers in yeast

In a recent paper [181] (trailed earlier [4]), we exploited the fact that the early systematic sequencing of the *S. cerevisiae* genome [182,183] allowed the production of a series of bar-coded mutant strains that individually lacked one (or both alleles in the homozygous diploid deletant) of each of the protein products encoded in that organism's genome [184–186]. The fraction and identity of those that are carriers is known from genomic (and in some cases biochemical) analyses. We could therefore exploit the fact that if we could add a drug that was toxic at a certain concentration (we chose a concentration that had been determined to decrease the rate of growth of the wild type by 90%) we could detect which strains were more resistant to the drugs, and thereby determine those strains that lacked the specific carriers whose decreased concentrations provided or improved resistance (Fig. 2). We could then test those strains directly and individually relative to the wild type and thereby establish, by single-gene differences, those that were presumably carriers of the drugs. Further evidence for this came from the ability of known natural substrates of those carriers to compete for uptake with the drug and thereby relieve its toxicity. This is very straightforward evidence indeed, and in most cases tested we found very clear evidence for multiple carriers with varying degrees of effectiveness in lowering the toxicity (in deletion strains) of the drugs tested, presumably by decreasing the uptake that was normally affected when the carrier was present. Figure 3 provides an example using diphenylethylideneiodonium, an NAD(P)H oxidase inhibitor [187,188] that seems to be taken up

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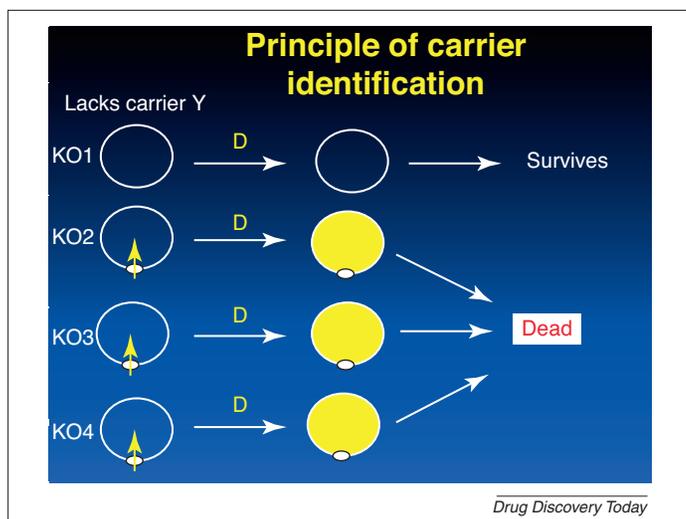


FIGURE 2

The principle of assessing carriers involved in drug uptake using the bar-coded yeast deletion strain collection [4,181]. Strains are competed against each other in a growth assay in the presence of a concentration of a drug that decreases the growth rate of the wild type by 90%. Strains (the lower three in the figure) expressing a carrier for the toxic substance take it up and are more or less likely to be killed, whereas those that lack the relevant carrier (top strain) do not take up the substance via that carrier and are more resistant (albeit other carriers may still be used). The numbers of each strain surviving after a certain period are assessed via the binding of their specific barcodes to complementary sequences in a microarray (or by 'deep sequencing'). The 'individual' strains can then be tested directly in axenic culture. By performing such tests in parallel, however, we assess the relative importance of all carriers *in vivo* simultaneously.

predominantly by one transporter, whereas Fig. 4 displays some data for fluconazole, where four transporters are clearly detectable. These [181] are the kinds of experiments that make clear precisely which drugs use which transporters, without any 'speculation'. It is also important to note the use of multiple carriers by most of the different drugs [181], which explains in large measure why such carriers are not identified when absolute (qualitative) growth/no growth experiments are done with mutant strains lacking one of them, because deleting one still allows considerable flux through others. Only quantitative measurements of the type that we described [181] reflect the relative contributions of the multiple transporters. Of course this is not the first line of evidence for drug transporters, but the approach may be used more generally and the findings were unequivocal.

An example of multiple drug carriers detected through drug resistance studies in trypanosomes

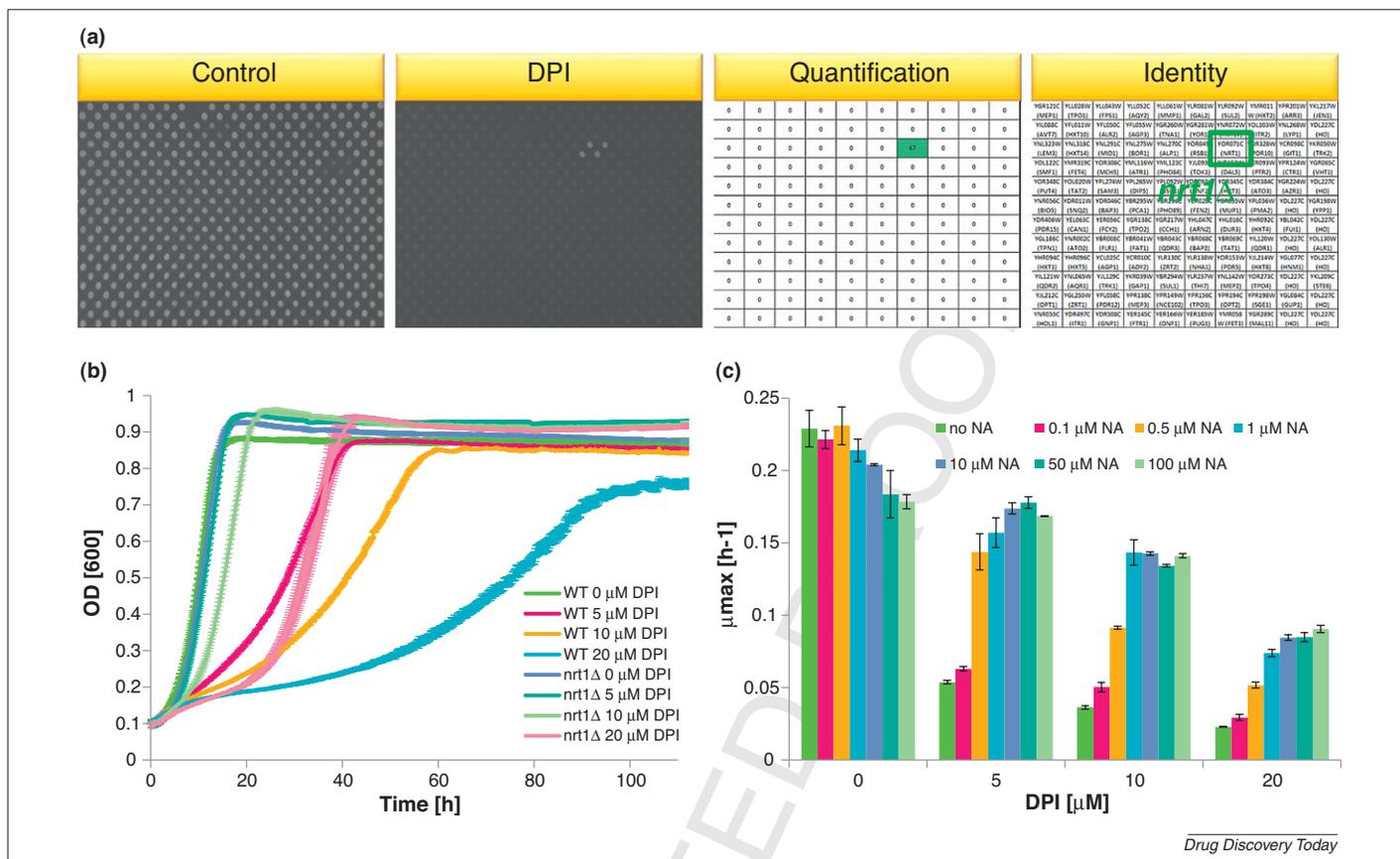
While we shall have to await more extensive pharmacogenomics studies in humans, where most drug carriers have native functions and deleterious mutations in the host tend not to be selected, there is a clear class of drug in which selection for resistance may be expected, and those are cases in which drugs are designed to kill the target organism. Trypanosomes such as *Trypanosoma brucei gambiense* or *T. brucei rhodesiense* are the causative agents of sleeping sickness, a typically fatal disease (in the absence of chemotherapy), and we use the resistance of trypanosomes to the arsenical drug melarsoprol and the diamidine drug pentamidine as an example. These two drugs have entirely separate modes of action,

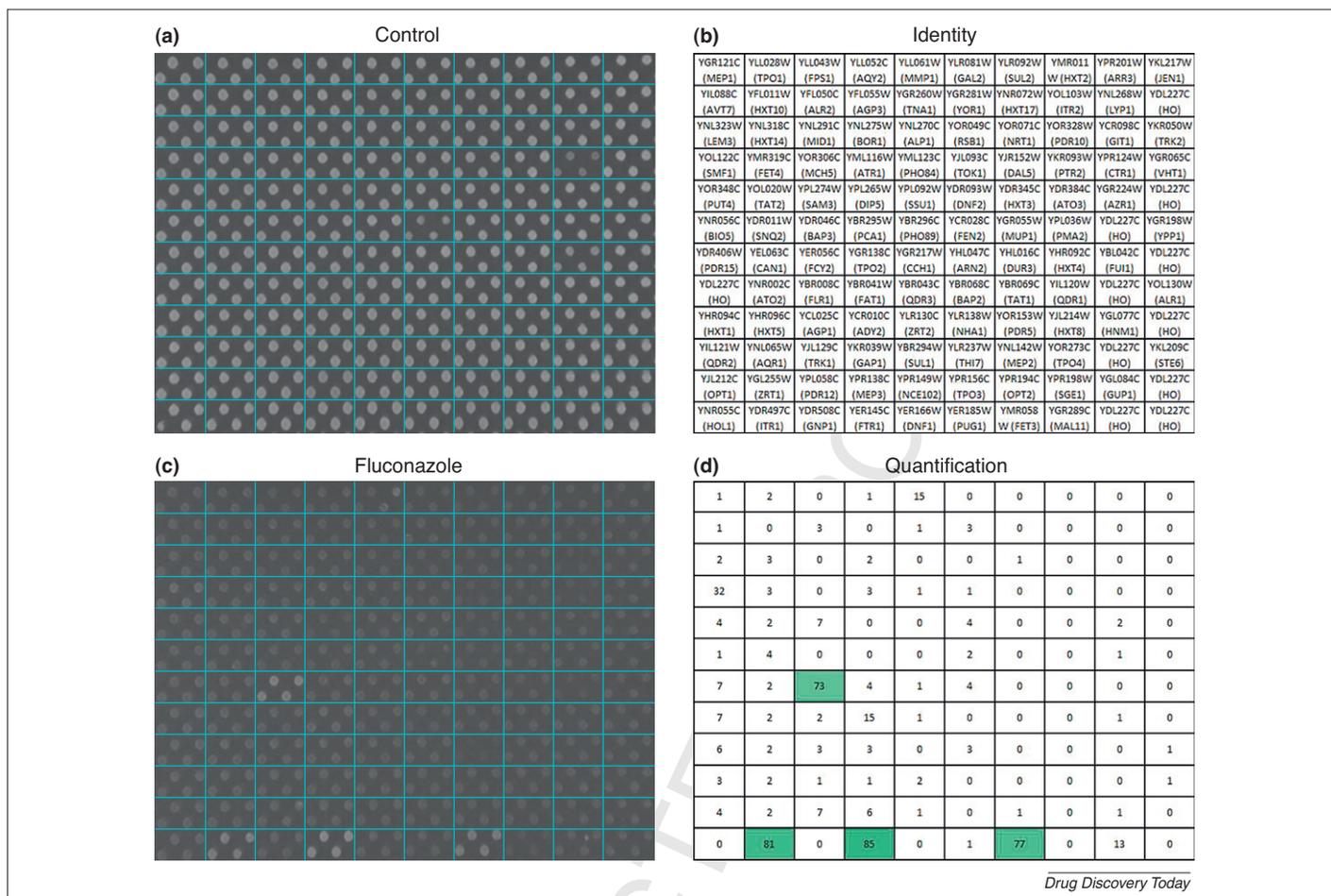
in that melarsoprol is thought to act mainly via the formation of a toxic trypanothione adduct known as Mel T [189,190], whereas pentamidine binds DNA and is concentrated in mitochondria where it disrupts free energy conservation [191]. Cross resistance to these two drugs might therefore not be expected to occur via mutations in their targets, but is nonetheless known [192], and is mediated in particular by a trypanosomal aquaglyceroporin 2 that works (whether directly or otherwise [190]) to transport them towards their cellular targets [193]. In addition, both pentamidine and melarsoprol are also transported via the adenosine transporter AT1 [194–200], pentamidine is transported using NT11.1 and NT12.1 [201] while the source of energy for concentrative pentamidine uptake is provided by three H⁺-ATPases HA1–3 [190] (a mitochondrial pentamidine uptake carrier is not yet known). Both melarsoprol [202] and pentamidine are also substrates for the multidrug ABC efflux transporter MRPA [203]. Thus we find multiple transporters capable of (with at least some being functionally necessary for) the transport of (and or resistance to) either or both of the antitrypanosomal drugs melarsoprol and pentamidine, a fact of considerable and demonstrable significance in the development of drug resistance in the target organisms. Transporter-mediated resistance to each of the three other major antitrypanosomal drugs (eflornithine, nifurtimox and suramin) is reviewed by Alford *et al.* [190].

Similar phenomena are found in other parasites such as *Leishmania* [204–206], while resistance to the antimalarial drug chloroquine is also mainly transporter-mediated [77,166,207–214]. Overall, genome-wide RNAi screens look to have considerable potential for unravelling and identifying the multiple drug transporters in parasites and other organisms [190,215–219].

Summary of other evidence for the use of named SLC transporters by drugs

Despite the extensive evidence gathered before in the references cited [1,5], Di *et al.* [7] claim that 'Although hundreds of carrier proteins exist in many organisms, it is unlikely that the majority of these transporters recognize drugs'. In fact, as we discuss below, most proteins bind to multiple drugs and drug-like substances. However, we do not have to speculate whether it is 'unlikely' because we know the SLC families [220,221] and could determine, for each one, whether they do or do not transport a known drug (and note that new discoveries continue to emerge [222]), and very many do [1,5,99,223–225]. We would also point out, however, that this is not the correct question because, if even just one transporter type affected major flux for all anionic drugs and another type, say, for all cationic drugs, that alone would be sufficient to account for the transport of drugs by carriers rather than via trans-phospholipid diffusion. Thus, the more pertinent question is not 'do all transporters recognise a drug?' but 'do all drugs recognise a transporter?' To answer this, we can take both a generic and a more specific approach. The generic approach uses electronic means [8,226] to query the public databases (some are listed in Table 1) as to whether one or more carriers is known for each known drug. Of course in many cases the specific interest hinges upon those drugs that are seen as most 'important' as judged for instance by sales, and we have therefore investigated each of the 'top 10' small-molecule drugs by sales (amounting, in 2010, to some US\$63Bn). As shown in Table 2, there is evidence





Drug Discovery Today

FIGURE 4

Identification and validation of fluconazole transporters. The experiment was performed as in Fig. 3a. In this case, the deletion of any of four transporter genes (*ITR1*, *FTR1*, *FET3*, and *FCY2*) provides resistance to the antifungal drug, indicating that they may all contribute to the uptake of fluconazole.

(<http://www.proteinatlas.org/>). This expression profiling evidence is an important component of the evidence necessary for determining which protein carriers might be used in specific tissues. As phrased by Sprowl *et al.* [98] ‘Considering the sheer magnitude of the number of transporters in humans identified thus far, it is not hard to imagine that the work done so far can only represent, at best, the tip of the iceberg’.

Di *et al.* [7] make much of an expression profiling study [253] in which it is found that there is a correlation coefficient of 0.85 between the jejunal and Caco-2 permeabilities of various drugs when ‘removing compounds that are mainly transported by carrier-mediated processes’. While a study of 12,000 gene tags, 443 carriers and no proper hold-out set is not capable of explaining robustly [272,273] the permeability properties of just 26 drugs, our focus lies on the drugs studied. Specifically, the list of compounds that were not removed, and thus presumably taken to lack significant interactions with carriers, is as follows, but now with non-exhaustive references added by us to show that all of them possess, or interact with, known (and, often, multiple) transporters: furosemide (six transporters, e.g. <http://www.drugbank.ca/drugs/DB00695#transporters>, [274,275]), hydrochlorothiazide [275–280], atenolol [281–284]; cimetidine (12 transporters <http://www.drugbank.ca/drugs/DB00501#transporters>, e.g. [60,164,285–294]), mannitol (believed to be transported, if at all, via a

paracellular route [295–297]), terbutaline [294], metoprolol [298–300], propranolol [299–304], desipramine [305–307], piroxicam [308–315], ketoprofen [312,314,316–318] and naproxen [308,312,316,319].

As before (Fig. 2b of [5]), we would point out that claims about the absence (or that ignore the presence) of a transporter interacting with a named drug may often be dismissed following a simple literature search or an inspection of public databases [320–322] such as DrugBank (<http://www.drugbank.ca/>) or others in Table 1 and elsewhere. Contrary to the claim of Di *et al.* [7], therefore, analysis of the paper by Sun *et al.* [253] does not at all ‘suggest that passive diffusion is the major mechanism for the uptake of the compounds rather than carrier-mediated processes’ [7], because – apart from mannitol, whose role is precisely to act as an osmoticum – we could find evidence for transporters interacting with ‘each’ of the compounds mentioned.

Di and colleagues [7] drew attention to a study of 197 drugs by Tsinman and colleagues [323] in a paper designed to promote an artificial membrane method (again with all the slopes in log–log plots significantly below unity – see previous discussion [5]). However, most of these 197 drugs (listed in Table 1 of that paper) also have known interactions with carriers (for reasons of space we do not, in this case list, all the references). Consequently, it is not clear what understanding such studies in artificial systems can

TABLE 1

Some web-accessible resources for assessing (potentially promiscuous) drug–target (including drug–transporter) interactions ('drug' here often meaning small molecule ligand rather than licensed drug)

Database	URL	Drugs	Targets	Reference
BindingDB	http://www.bindingdb.org/bind/index.jsp	>180,000	3673	[520]
ChEBI	http://www.ebi.ac.uk/chebi/init.do	>28,000		[521]
ChEMBL	https://www.ebi.ac.uk/chembl/db/	>1 million	>8800	[522]
ChemProt	http://www.cbs.dtu.dk/services/ChemProt/	>700,000	>30,000	[523]
ChemSpider	http://www.chemspider.com/	>26 million	None	[321]
DRAR-CPI	http://cpi.bio-x.cn/drar/			[492]
Drug Adverse Reaction Target Database	http://xin.cz3.nus.edu.sg/group/drt/dart.asp	1080	236	[524]
DrugBank	http://www.drugbank.ca/	6711	4227	[525]
iPHACE	http://cgl.imim.es/iphace/	739	181	[394]
MATADOR	http://matador.embl.de/	775		[147]
PDSPKi	http://pdsp.med.unc.edu/kidb.php			[526]
PharmGKB	http://www.pharmgkb.org/			[527]
Potential Drug Target Database (PDTD)	http://www.dddc.ac.cn/pdtd/	–	841	[528]
PROCOGNATE	http://www.ebi.ac.uk/thorntonsrv/databases/procognate/			[529]
PROMISCUOUS	http://bioinformatics.charite.de/promiscuous/	>25,000		[393]
PubChem	http://pubchem.ncbi.nlm.nih.gov/	>31 million	>1600 assays	[530]
PubChem promiscuity	http://chemutils.florida.scripps.edu/pcpromiscuity			[531]
SePreSA	http://sepresa.bio-x.cn/			[532]
SIDER2	http://sideeffects.embl.de/	996	4199	[533]
SuperTarget	http://bioinformatics.charite.de/supertarget/	195,770	6219	[150]
TarFisDock	http://www.dddc.ac.cn/tarfisdock			[375]
TDR Targets	http://tdrtargets.org	825,814		[534]
Therapeutic Target Database (TTD)	http://bidd.nus.edu.sg/group/tdt/	17,816	2015	[535]
Toxin, toxin-target database (T3DB)	http://www.t3db.org/	2900	1300	[536]
Transporter Classification DataBase (TCDB)	http://tcdb.org/			[537]

Some others are listed, for example in [457,538,539]. Other commercial offerings also exist, including Bioprint/Cerep [370].

bring to the question of which carriers are used by specific drugs in biological membranes, and how that affects their distribution in living cells and organisms.

So what precisely do we need to measure (or simulate)?

Given the availability of approximate metabolic networks [237,239,324], including tissue-specific versions [325,326], the only other data required to produce a reasonably accurate systems biology (ordinary differential equation) model are those for the concentrations of the enzymes in each tissue and their approximate kinetics for the substrates of interest.

The blood–brain barrier (BBB)

The BBB (hence the name) is widely recognised as being comparatively impermeable to most drugs that can enter other cells [327–341]. Certainly the BBB lacks paracellular transport and is known to contain a number of efflux pumps [333,335,342,343]. However, since, so far as we know, the phospholipids existing in membranes contributing to the BBB do not differ materially from those in other mammalian cells or tissues, it is of interest to seek to understand why these phospholipids are now impermeable to drugs whose uptake is supposed to be mediated normally via the

phospholipid bilayers; Di and colleagues [7] do not comment, but the most plausible explanation [5] is simply that drug transport *in vivo* does not occur via phospholipid bilayers at non-negligible rates. Here we analyse a few of the claims of Di and colleagues [7] regarding the BBB.

***'The BBB uptake transporters have unique substrate specificities and require specific structural motifs for transportation to be possible.'* [7]**

It is not clear what is meant here, since probably no transporter has a 'unique substrate specificity' in the sense of binding and transporting only a single molecular type (but all have an identifiable pattern of substrate specificities, including some that are rather specific relative to the considerable promiscuity of many others – see the numerous comments on promiscuity, above). In fact, the evidence for substrate promiscuity is overwhelming, and is highlighted in many places here and elsewhere. We would certainly agree that it is well established that there are many SLCs expressed in the BBB, as a small sampling of review references [34,327,329,330,335,337,339,344–348], and many others given before [1,5], indicates. These show exactly which kinds of transporters are present in the BBB. Although such information might

REVIEWS

TABLE 2

Interaction of 'blockbuster' small molecule drugs with known transporters.

Drug name	Disease area	Annual Sales (2010) in \$Bn	Known transporter (family) interaction(s)	Representative references
Lipitor (atorvastatin)	Cardiovascular	10.7	ABCB1 ABCC1 ABCC4 ABCC5 ABCG2 SLCO1A2 SLCO1B1	[94,489,540–546]
Plavix (clopidogrel)	Cardiovascular	9.5	ABCB1	[547–550]
Seretide/Advair (salmeterol xinafoate/fluticasone propionate)	Pulmonary (COPD)	8.3	ABCB1 SLC22A2 SLC22A3	[25,551–554]
Diovan (valsartan)	Cardiovascular	6.1	OATP 1B1 SLCO1B3 SLC22A9	[27,555–560]

TABLE 2 (Continued)

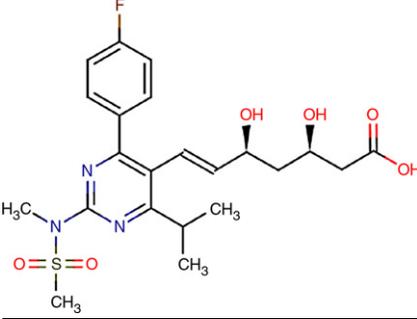
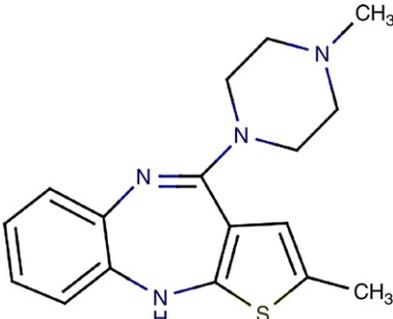
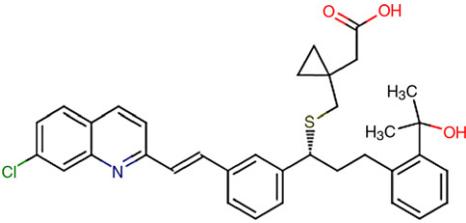
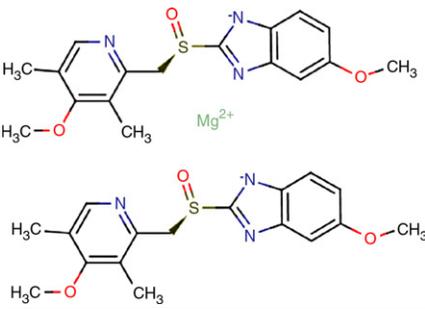
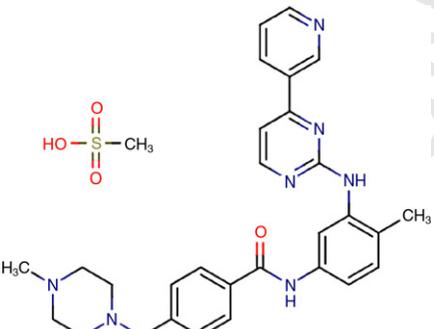
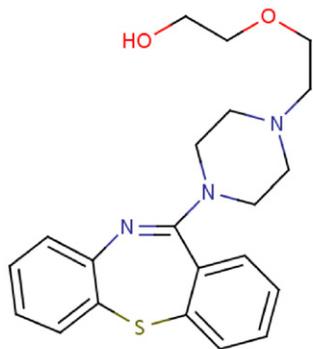
Drug name	Disease area	Annual Sales (2010) in \$Bn	Known transporter (family) interaction(s)	Representative references
Crestor (rosuvastatin) 	Cardiovascular	5.7	ABCC1 ABCC4 ABCG2 SLCO1A2 SLCO1B1 SLCO1B3	[27,94,489,541–544, 546,561–564]
Zyprexa (olanzapine) 	CNS	5.1	ABCB1 SLC6A2	[565–567]
Singulair (montelukast) 	Allergy	5.0	ABCB1 SLCO2B1	[568–572]
Nexium (esomeprazole) 	Gastrointestinal	5.0	H ⁺ -K ⁺ -ATPase (target) ATP4A	[573,574]
Gleevec (imatinib) 	Cancer	4.3	ABCA3 ABCB1 ABCC4 ABCG2 SLC22A1 SLC22A2	[575–584]

TABLE 2 (Continued)

Drug name	Disease area	Annual Sales (2010) in \$Bn	Known transporter (family) interaction(s)	Representative references
Seroquel (quetiapine)	CNS	4.1	ABCB1	[362,565,585,586]



The 'top 10' small molecule blockbuster data are taken from the LaMerie website (http://www.pipelinereview.com/free-downloads/blockbuster_drugs_2010.pdf). Other data from literature searches or (including structures) via DrugBank (<http://www.drugbank.ca/>), ChEBI (<http://www.ebi.ac.uk/chebi/init.do>), ChEMBL (<https://www.ebi.ac.uk/chembl/db/>), ChemSpider (<http://www.chemspider.com/>) or KEGGDrug (<http://www.genome.jp/kegg/drug/>). It may be noted that each of the ten drugs interacts with at least one known transporter. The total sales of these drugs in 2010 amounted to \$63.7Bn.

sensibly be exploited [34] to get drugs into the CNS, Di and colleagues [7] doubt this:

'Prodrug approaches that use uptake transporters to increase brain penetration are scarce and have limited success' [7]

While we have cited many papers and reviews showing examples of the exploitation of known BBB solute transport carriers in assisting CNS uptake [1,5], we can add a few other reviews [34,330,337,338,349–352] and papers, such as ones exploiting the large amino acid transporter [353–356], the neutral/cationic amino acid transporter [357], the glucose transporter [354,358,359], the ascorbate transporter [337,360], and the organic cation [361,362], anion [346,363], choline [364–366] and monocarboxylate [346] transporters, a monoamine transporter [367], and a H⁺-amine antiporter [368]. Indeed, 'Use of endogenous transport systems is the great, untapped strategy in drug delivery to the brain' [338], with the substrates of many highly expressed transporters yet to be determined [369].

'By contrast, there is a large body of strong evidence that suggests many lipophilic small molecules cross the BBB by passive diffusion.' [7]

Actually, there is no such evidence, merely an interpretation of various kinds of data (see e.g. [272,273] for why these are not at all the same thing), not least because these kinds of studies mainly seek to correlate some measure of lipophilicity with net uptake. This is probably a pointless exercise for at least two main reasons:

- (i) We do not yet know the substrate specificities of all the influx and efflux transporters in the BBB, and lipophilicity is known to correlate quite well with the effectiveness of drug 'efflux' carriers, which obviously then compromises any assessment of the effect of lipophilicity on drug 'uptake';
- (ii) lipophilicity is also known to correlate with many things that have nothing at all to do with diffusion through phospholipids, for example, the binding of molecules to the water-soluble protein luciferase, see below.

However, we can at least say that if increased lipophilicity caused improved transport of drugs through phospholipid bilayers in biological cells, it would be most obvious for roughly homologous series in which a specific pharmacophore was made more lipophilic. However, 'in actual practice, the reformulation of a water soluble drug with lipidization modifications is difficult to execute successfully, and there is not a single example of a drug presently sold whereby medicinal chemistry was successfully used to convert a non-brain-penetrating drug into a molecule that crosses the BBB in pharmacologically significant amounts' [329].

'This analysis predicts that a large fraction of solute-transporting proteins with unknown function will probably not transport substrates the size of drugs.' [7]

Even leaving aside the many SLC transporters of 'known' function, and as discussed throughout this article with regard to the promiscuity of drug binding, this prediction is simply not borne out by the facts, whether for the BBB or in other tissues. We give some more examples below.

Related areas concerning the interaction of drugs with multiple proteins and how they have been informed by new facts

Promiscuity of drug binding to proteins, and its relationship to lipophilicity

Since some of the arguments we have raised imply that most drugs are likely to bind to (or hitchhike on) multiple transporters, it is worth having a look at how common the promiscuity of protein binding is for known drugs (and drug-like molecules). A straightforward analysis of the literature shows that it is becoming increasingly clear that individual drugs [71,370–412], and even intermediary metabolites [413–416], do experimentally bind to very many more entities than just the single 'target' via which they were typically discovered. An analysis (<http://www.bindingdb.org/bind/ByMonomersTarget.jsp>) shows that of 3673 targets, just 400 have only one known ligand, with the rest therefore being

promiscuous. The number of targets with at least ten known (experimentally measured) ligands is 2323, with the ‘winner’ being a dopamine receptor with no fewer than 7317 experimentally measured ligands. Such promiscuous or ‘off-target’ binding (whether seen as ‘real’ or ‘adventitious’, and see also Table 2) is typically a function of lipophilicity [371,387,391,393,395,396,410,417–421] or size [386,422]. It is underpinned by the biophysics of binding to just 20 main amino acids, and the finite number of known protein folds that are reused [423] and thus bear an evolutionary relationship to each other [145,412]. On average, drugs are known to interact with no fewer than six targets [419], and many proteins are known to interact with hundreds of drugs [376]. Indeed, polypharmacology and off-target effects are probably the rule and not the exception for the discovery of effective drugs [9,372,374,376,383,385,386,405,411,424–429]. Equally, if off-target effects are unfavourable, this can have an important bearing on toxicity. We next give two examples of such promiscuity or polypharmacology. (A discussion of the ‘off-target’ effects of statins and glitazones appears elsewhere [9].) Overall, what is clear is that there is abundant and increasing evidence for drugs interacting with large numbers of proteins, partly according to their lipophilicity.

General anaesthetics (narcotics)

As we have mentioned before [1,5], and here update, there is another major class of compounds whose mode of action was closely related to their lipophilicity, and it was believed [430] (mainly because of the lack of a clear molecular structure–activity relationship) to function solely via phospholipids. These are the general anaesthetics or narcotics. However, it is now entirely clear [431–448] that they bind, relatively specifically, to hydrophobic pockets within protein receptors or targets, whether functional or not, and that this alone can account for their actions. The binding of bromoform to luciferase is shown in Fig. 5. Examples such as the essential resistance to otherwise fully narcotising concentrations of inhalational anaesthetics, such as halothane in TREK K⁺ channel mouse knockouts [434,435], provides just the kind of genetic evidence necessary to clarify the crucial role of such proteins in inhalational anaesthesia that we are here proposing for drug transporter studies.

QSAR of molecules binding to and affecting the hERG channel

The statement is made [7] that ‘The extent to which the transporters can recognize drug molecules in addition to their endogenous substrates is, at best, questionable’. This statement completely ignores the facts of (i) the massively wide recognition (it underpins the whole basis of QSAR studies [449–451]) that individual proteins can bind any number of molecules (e.g. [452] and vice versa [419], and see above), and (ii) that ion and neurotransmitter transporters are an important target class for pharmaceutical drugs [42,376,453–455]. To this end, it is worth pointing out that ion channel or drug transporter molecules are well represented among the (purported) targets of marketed drugs [456,457].

Another protein receptor (and ion transporter) with a wide affinity for more or less lipophilic drugs, and of well known and considerable significance in the pharmaceutical industry (and certainly not ‘at best questionable’), is the hERG channel, that

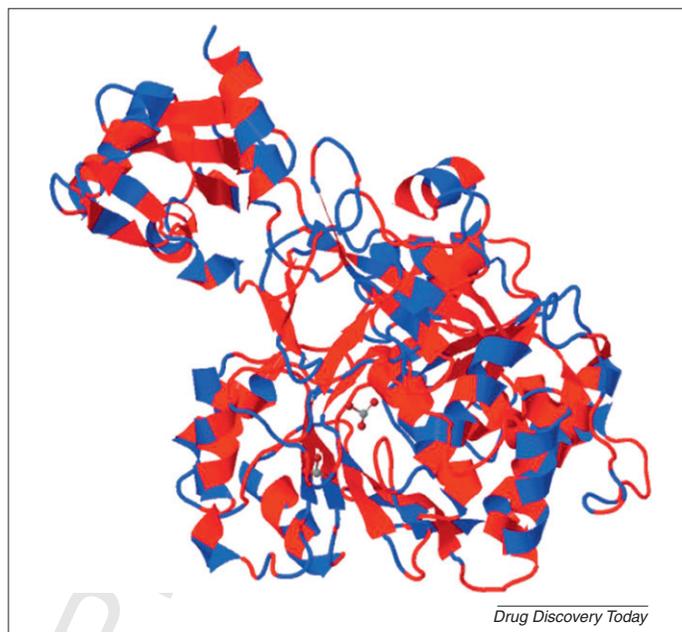


FIGURE 5

The binding of bromoform to a hydrophobic pocket of the water-soluble enzyme luciferase [431]. The picture (with protein side chain hydrophobicity encoded in red) is derived from the data deposited at the protein databank (PDB reference 1BA3; <http://www.rcsb.org/pdb/explore/jmol.do?structureId=1BA3&opt=3>). Two bromoform molecules (with carbon in grey and Br in red) are bound and may be observed.

is, the ‘human ether-a-go-go-related’ hERG-encoded cardiac K⁺ channel. As is well known, this molecule may bind to, and be affected by, a very large number of drugs ([408], and <http://bindingdb.org> lists over 3800 hits), with potential and dangerous prolongation of the QT phase of cardiac performance as detected via electrophysiology [458–463]. Here again there is little doubt, typically from electrophysiological evidence, of the functional relationship between the binding of drugs of very different structural properties, their lipophilicity/hydrophobicity, and their ability to inhibit the hERG channel [300,464–476].

While we could write a very large survey on the fact that individual drugs (whether designed to or otherwise) interact with a great many targets, and specific targets interact with a great many drugs, especially as a function of their lipophilicity, the two well-known examples in this section are probably sufficient to remind readers that this is so, and is so more generally. In particular, those who doubt it can survey the facts in the databases listed in Table 1. However, it is worth rehearsing another highly important area [477–479] of drug–drug interactions that realistically can only be effected via interactions with proteins, such as transporters, rather than phospholipids, and this is the area of adverse drug reactions.

Adverse drug reactions as off-target effects

Just as it is hard to envisage significant competition between molecules at low concentrations for the ability to cross phospholipid bilayers, the competitive (and indeed uncompetitive and non-competitive) interaction of small molecules with each other via binding and modulation of protein-mediated activities lies at the core of enzymology. This is again manifested as a kind of

'promiscuity' in which one protein interacts with multiple small molecules.

In a similar way, the binding of individual molecules to multiple proteins or targets, as well as providing opportunities in polypharmacology, can lead to some off-target effects that are undesirable; these are commonly referred to as 'adverse drug reactions' (e.g. [71,75,91,156,377,394,408,453,480–494]), and provide a further class of evidence for considerable and important drug promiscuity, including interactions with transporters.

Systems pharmacology

The overall result of these considerations, then, is the recognition that we need proper (quantitative and mathematical) models of the interactions between drugs and their multiple targets and binding partners, including transporters. This field is emerging as Network or Systems Pharmacology/Medicine [41,93,229,230, 234,235,238,379,426,484,488,495–514]. Without these kinds of approaches, we shall continue to fail to identify the mechanistic basis for the transfer of drugs across biological membranes.

Concluding remarks

As previously [5], we find it useful to summarise the issues in a number of bullet points since, as Di and colleagues [7] comment (and we agree), understanding the means by which drugs reach their targets 'has a major impact on the strategic decisions in drug discovery and development'.

- There is overwhelming evidence, wherever it is sought, that drugs use transporter molecules to get into and out of cells.
- The question to be asked should not be 'do all transporters recognise a drug?' but 'do all drugs recognise a transporter (or many transporters) and, if so, which one(s)?'
- A recently described system in baker's yeast allows one to evaluate all drug transporters (and other enzymes) in parallel, and thereby to establish which drugs use which transporters
- Carriers are no different from other enzymes that effect chemical transformations in that they obey standard enzyme kinetic laws. These include principles such as the dependence of their rates on substrate, product, effector, and transporter concentrations (and including any free energy coupling), a dependence on pH (via ionisation changes in both substrates and enzyme), and constraints on forward and back reactions as described by the Haldane relation.
- Many, and probably all, enzymes are rather promiscuous and can bind to and effect catalysis on multiple substrates,

including hydrophobic/lipophilic ones. Well-known examples of interest here include efflux and influx transporters, drug-metabolising enzymes, general anaesthetics, and the hERG channel

- The common and substantial promiscuity of receptors for small molecules underpins the whole of QSAR studies, and transporters and ion channels are an important class of drug targets that are equivalently promiscuous
- For evolutionary, as well as biophysical, reasons most small molecules interact with multiple proteins, and are thus also promiscuous.
- It is not wise to claim that any particular drug interacts solely with its nominal target without looking at the literature (including online databases) carefully first. In most cases, one can find evidence for at least one transporter (and often many) with which it also interacts.
- Promiscuity of protein binding is commonly related to lipophilicity, and so is an inadequate measure for assessing whether such interactions are also (let alone solely) occurring with phospholipids.
- Drug promiscuity, by which drugs bind to a wide variety of targets, is very widespread, almost to the point of universality. Such so-called 'off-target' effects may be useful or otherwise, but they are commonplace. Thus it is entirely expected (and found) that drugs can bind to multiple proteins, including transporters. Hundreds of examples show that they do so.

Drug uptake into cells is very largely, if not indeed exclusively (though that cannot be proved), via proteinaceous carriers. Their transport *in vivo* via phospholipid bilayers is thus negligible. A recognition of this fact indicates that we need to produce proper systems biology models of the human metabolic and signalling networks. This should also have a massively beneficial effect on the increasingly low productivity and appalling attrition rates [495,515–518] that are still widely suffered by the pharmaceutical industry

Competing financial interests

The authors have in the past had funding from GSK, as described in their published studies of drug transporters in yeast cells. The authors have no present competing financial interests.

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References

- 1 Dobson, P.D. and Kell, D.B. (2008) Carrier-mediated cellular uptake of pharmaceutical drugs: an exception or the rule? *Nat. Rev. Drug Discov.* 7, 205–220
- 2 Dobson, P.D. *et al.* (2009) 'Metabolite-likeness' as a criterion in the design and selection of pharmaceutical drug libraries. *Drug Discov. Today* 14, 31–40
- 3 Dobson, P. *et al.* (2009) Implications of the dominant role of cellular transporters in drug uptake. *Curr. Top. Med. Chem.* 9, 163–184
- 4 Kell, D.B. and Dobson, P.D. (2009) The cellular uptake of pharmaceutical drugs is mainly carrier-mediated and is thus an issue not so much of biophysics but of systems biology. In *Proc. Int. Beilstein Symposium on Systems Chemistry* (Hicks, M.G. and Kettner, C., eds), pp. 149–168, Logos Verlag
- 5 Kell, D.B. *et al.* (2011) Pharmaceutical drug transport: the issues and the implications that it is essentially carrier-mediated only. *Drug Discov. Today* 16, 704–714
- 6 Sugano, K. *et al.* (2010) Coexistence of passive and carrier-mediated processes in drug transport. *Nat. Rev. Drug Discov.* 9, 597–614
- 7 Di, L. *et al.* (2012) Evidence-based approach to assess passive diffusion and carrier-mediated drug transport. *Drug Discov. Today* 17, 905–912
- 8 Hull, D. *et al.* (2008) Defrosting the digital library: bibliographic tools for the next generation web. *PLoS Comput. Biol.* 4, E1000204 1000210.1001371/journal.pcbi.1000204

- 9 Kell, D.B. (2009) Iron behaving badly: inappropriate iron chelation as a major contributor to the aetiology of vascular and other progressive inflammatory and degenerative diseases. *BMC Med. Genom.* 2, 2
- 10 Kell, D.B. (2010) Towards a unifying, systems biology understanding of large-scale cellular death and destruction caused by poorly liganded iron: Parkinson's, Huntington's, Alzheimer's, prions, bactericides, chemical toxicology and others as examples. *Arch. Toxicol.* 577, 825–889 10.1007/s00204-00010-00577-x
- 11 Endres, C.J. *et al.* (2006) The role of transporters in drug interactions. *Eur. J. Pharm. Sci.* 27, 501–517
- 12 Evseenko, D. *et al.* (2006) Active transport across the human placenta: impact on drug efficacy and toxicity. *Expert Opin. Drug Metab. Toxicol.* 2, 51–69
- 13 Rizwan, A.N. and Burckhardt, G. (2007) Organic anion transporters of the SLC22 family: biopharmaceutical, physiological, and pathological roles. *Pharm. Res.* 24, 450–470
- 14 Rostami-Hodjegan, A. and Tucker, G.T. (2007) Simulation and prediction of *in vivo* drug metabolism in human populations from *in vitro* data. *Nat. Rev. Drug Discov.* 6, 140–148
- 15 Bhardwaj, R.K. *et al.* (2008) Intestinal transporters in drug absorption. In *Biopharmaceutics Applications in Drug Development* (Krishna, R. and Yu, L., eds), pp. 175–261, Springer
- 16 Terada, T. and Inui, K. (2008) Physiological and pharmacokinetic roles of H⁺/organic cation antiporters (MATE/SLC47A). *Biochem. Pharmacol.* 75, 1689–1696
- 17 Jamei, M. *et al.* (2009) A framework for assessing inter-individual variability in pharmacokinetics using virtual human populations and integrating general knowledge of physical chemistry, biology, anatomy, physiology and genetics: a tale of 'bottom-up' vs 'top-down' recognition of covariates. *Drug Metab. Pharmacokinet.* 24, 53–75
- 18 Kalliokoski, A. and Niemi, M. (2009) Impact of OATP transporters on pharmacokinetics. *Br. J. Pharmacol.* 158, 693–705
- 19 Rees, D.C. *et al.* (2009) ABC transporters: the power to change. *Nat. Rev. Mol. Cell Biol.* 10, 218–227
- 20 Shugarts, S. and Benet, L.Z. (2009) The role of transporters in the pharmacokinetics of orally administered drugs. *Pharm. Res.* 26, 2039–2054
- 21 Vähäkangas, K. and Myllynen, P. (2009) Drug transporters in the human blood–placental barrier. *Br. J. Pharmacol.* 158, 665–678
- 22 Welsh, M. *et al.* (2009) Pharmacogenomic discovery using cell-based models. *Pharmacol. Rev.* 61, 413–429
- 23 Anderson, C.M. and Thwaites, D.T. (2010) Hijacking solute carriers for proton-coupled drug transport. *Physiology (Bethesda)* 25, 364–377
- 24 Benet, L.Z. (2010) Predicting drug disposition via application of a Biopharmaceutics Drug Disposition Classification System. *Basic Clin. Pharmacol. Toxicol.* 106, 162–167
- 25 Bosquillon, C. (2010) Drug transporters in the lung – do they play a role in the biopharmaceutics of inhaled drugs? *J. Pharm. Sci.* 99, 2240–2255
- 26 Darwich, A.S. *et al.* (2010) Interplay of metabolism and transport in determining oral drug absorption and gut wall metabolism: a simulation assessment using the 'Advanced Dissolution, Absorption, Metabolism (ADAM)' model. *Curr. Drug Metab.* 11, 716–729
- 27 Fahrmar, C. *et al.* (2010) Hepatic OATP and OCT uptake transporters: their role for drug–drug interactions and pharmacogenetic aspects. *Drug Metab. Rev.* 42, 380–401
- 28 Giacomini, K.M. *et al.* (2010) Membrane transporters in drug development. *Nat. Rev. Drug Discov.* 9, 215–236
- 29 Hagos, Y. and Wolff, N.A. (2010) Assessment of the role of renal organic anion transporters in drug-induced nephrotoxicity. *Toxins (Basel)* 2, 2055–2082
- 30 Ho, R.H. and Kim, R.B. (2010) Drug Transporters. In *Handbook of Drug–Nutrient Interactions*. (2nd edn), pp. 45–84
- 31 Huang, S.M. *et al.* (2010) The International Transporter Consortium: a collaborative group of scientists from academia, industry, and the FDA. *Clin. Pharmacol. Ther.* 87, 32–36
- 32 Kis, O. *et al.* (2010) The complexities of antiretroviral drug–drug interactions: role of ABC and SLC transporters. *Trends Pharmacol. Sci.* 31, 22–35
- 33 Maeda, K. and Sugiyama, Y. (2010) The use of hepatocytes to investigate drug uptake transporters. *Hepatocytes: Methods Protoc.* 640, 327–353
- 34 Mittapalli, R.K. *et al.* (2010) Exploiting nutrient transporters at the blood–brain barrier to improve brain distribution of small molecules. *Therapeutic Deliv.* 1, 775–784
- 35 Pang, K.S. *et al.* eds (2010) *Enzyme- and Transporter-Based Drug–Drug Interactions: Progress and Future Challenges*, Springer
- 36 Russel, F.G.M. (2010) Transporters: importance in drug absorption, distribution, and removal. In *Enzyme- and Transporter-Based Drug–Drug Interactions: Progress and Future Challenges*. pp. 27–49
- 37 Schlessinger, A. *et al.* (2010) Comparison of human solute carriers. *Protein Sci.* 19, 412–428
- 38 VanWert, A.L. *et al.* (2010) Organic anion transporters: discovery, pharmacology, regulation and roles in pathophysiology. *Biopharm. Drug Dispos.* 31, 1–71
- 39 Varma, M.V. *et al.* (2010) Targeting intestinal transporters for optimizing oral drug absorption. *Curr. Drug Metab.* 11, 730–742
- 40 Zhang, L. *et al.* (2010) Drug interactions evaluation: an integrated part of risk assessment of therapeutics. *Toxicol. Appl. Pharmacol.* 243, 134–145
- 41 Ahn, S.Y. *et al.* (2011) Linkage of organic anion transporter-1 to metabolic pathways through integrated 'omics'-driven network and functional analysis. *J. Biol. Chem.* 286, 31522–31531
- 42 Alexander, S.P.H. *et al.* (2011) Guide to Receptors and Channels (GRAC), 5th edition. *Br. J. Pharmacol.* 164 (Suppl. 1), S1–S324
- 43 Benet, L.Z. *et al.* (2011) BDDCS applied to over 900 drugs. *AAPS J.* 13, 519–547
- 44 Burger, H. *et al.* (2011) Drug transporters of platinum-based anticancer agents and their clinical significance. *Drug Resist. Updat.* 14, 22–34
- 45 Choi, Y.H. *et al.* (2011) Herb–drug interactions: focus on metabolic enzymes and transporters. *Arch. Pharm. Res.* 34, 1843–1863
- 46 Cutler, M.J. and Choo, E.F. (2011) Overview of SLC22A and SLCO families of drug uptake transporters in the context of cancer treatments. *Curr. Drug Metab.* 12, 793–807
- 47 Dawson, P.A. (2011) Role of the intestinal bile acid transporters in bile acid and drug disposition. *Handb. Exp. Pharmacol.* 201, 169–203
- 48 Fromm, M.F. and Kim, R.B., eds (2011) *Drug Transporters*, Springer
- 49 Griffin, L. *et al.* (2011) Influence of drug transport proteins on the pharmacokinetics and drug interactions of HIV protease inhibitors. *J. Pharm. Sci.* 100, 3636–3654
- 50 Han, H.K. (2011) Role of transporters in drug interactions. *Arch. Pharm. Res.* 34, 1865–1877
- 51 Kemp, S. *et al.* (2011) Mammalian peroxisomal ABC transporters: from endogenous substrates to pathology and clinical significance. *Br. J. Pharmacol.* 164, 1753–1766
- 52 Klatt, S. *et al.* (2011) Transporter-mediated drug–drug interactions with oral antidiabetic drugs. *Pharmaceutics* 3, 680–705
- 53 Marzolini, C. *et al.* (2011) Mechanisms of drug interactions II: transport proteins. In *Drug Interactions in Infectious Diseases*. (3rd edn), pp. 43–72
- 54 Minuesa, G. *et al.* (2011) Drug uptake transporters in antiretroviral therapy. *Pharmacol. Ther.* 132, 268–279
- 55 Mruk, D.D. *et al.* (2011) Emerging role for drug transporters at the blood–testis barrier. *Trends Pharmacol. Sci.* 32, 99–106
- 56 Müller, F. and Fromm, M.F. (2011) Transporter-mediated drug–drug interactions. *Pharmacogenomics* 12, 1017–1037
- 57 Nakanishi, T. and Tamai, I. (2011) Solute carrier transporters as targets for drug delivery and pharmacological intervention for chemotherapy. *J. Pharm. Sci.* 100, 3731–3750
- 58 Ni, Z. and Mao, Q. (2011) ATP-binding cassette efflux transporters in human placenta. *Curr. Pharm. Biotechnol.* 12, 674–685
- 59 Niemi, M. *et al.* (2011) Organic anion transporting polypeptide 1B1: a genetically polymorphic transporter of major importance for hepatic drug uptake. *Pharmacol. Rev.* 63, 157–181
- 60 Nies, A.T. *et al.* (2011) Organic cation transporters (OCTs, MATEs), *in vitro* and *in vivo* evidence for the importance in drug therapy. *Handb. Exp. Pharmacol.* 201, 105–167
- 61 Shitara, Y. (2011) Clinical importance of OATP1B1 and OATP1B3 in drug–drug interactions. *Drug Metab. Pharmacokinet.* 26, 220–227
- 62 Su, L. *et al.* (2011) Drug transporters and blood–testis barrier function. *J. Endocrinol.* 209, 337–351
- 63 Svoboda, M. *et al.* (2011) Organic anion transporting polypeptides (OATPs): regulation of expression and function. *Curr. Drug Metab.* 12, 139–153
- 64 Thompson, T.N. (2011) The clinical significance of drug transporters in drug disposition and drug interactions. In *Pharmacokinetics in Drug Development, Vol. 3: Advances and Applications*. pp. 285–313
- 65 Thwaites, D.T. and Anderson, C.M.H. (2011) The SLC36 family of proton-coupled amino acid transporters and their potential role in drug transport. *Br. J. Pharmacol.* 164, 1802–1816
- 66 Tirona, R.G. (2011) Molecular mechanisms of drug transporter regulation. *Handb. Exp. Pharmacol.* 201, 373–402
- 67 Watanabe, T. *et al.* (2011) Prediction of the overall renal tubular secretion and hepatic clearance of anionic drugs and a renal drug–drug interaction involving organic anion transporter 3 in humans by *in vitro* uptake experiments. *Drug Metab. Dispos.* 39, 1031–1038

REVIEWS

- 68 Yamaguchi, H. *et al.* (2011) Screening of antibiotics that interact with organic anion-transporting polypeptides 1B1 and 1B3 using fluorescent probes. *Biol. Pharm. Bull.* 34, 389–395
- 69 Yonezawa, A. and Inui, K. (2011) Importance of the multidrug and toxin extrusion MATE/SLC47A family to pharmacokinetics, pharmacodynamics/toxicodynamics and pharmacogenomics. *Br. J. Pharmacol.* 164, 1817–1825
- 70 Zhang, L. *et al.* (2011) Transporter-mediated drug–drug interactions. *Clin. Pharmacol. Ther.* 89, 481–484
- 71 Zolk, O. and Fromm, M.F. (2011) Transporter-mediated drug uptake and efflux: important determinants of adverse drug reactions. *Clin. Pharmacol. Ther.* 89, 798–805
- 72 Bi, Y.A. *et al.* (2012) In vitro evaluation of hepatic transporter-mediated clinical drug–drug interactions: hepatocyte model optimization and retrospective investigation. *Drug Metab. Dispos.* 40, 1085–1092
- 73 Borbath, I. *et al.* (2012) Human equilibrative nucleoside transporter 1 (hENT1) expression is a potential predictive tool for response to gemcitabine in patients with advanced cholangiocarcinoma. *Eur. J. Cancer* 48, 990–996
- 74 Cheng, C.Y. and Mruk, D.D. (2012) The blood–testis barrier and its implications for male contraception. *Pharmacol. Rev.* 64, 16–64
- 75 Clarke, J.D. and Cherrington, N.J. (2012) Genetics or environment in drug transport: the case of organic anion transporting polypeptides and adverse drug reactions. *Expert Opin. Drug Metab. Toxicol.* 8, 349–360
- 76 DeGorter, M.K. *et al.* (2012) Drug transporters in drug efficacy and toxicity. *Annu. Rev. Pharmacol. Toxicol.* 52, 249–273
- 77 Delespau, V. and de Koning, H.P. (2012) Transporters in antiparasitic drug development and resistance. In *Antiparasitic and Antibacterial Drug Discovery: Trypanosomatidae* (Flohe, L. *et al.* eds), Wiley–Blackwell
- 78 Fardel, O. *et al.* (2012) Environmental chemicals as substrates, inhibitors or inducers of drug transporters: implication for toxicokinetics, toxicity and pharmacokinetics. *Expert Opin. Drug Metab. Toxicol.* 8, 29–46
- 79 Gallegos, T.F. *et al.* (2012) Organic anion and cation SLC22 ‘drug’ transporter (Oat1, Oat3, and Oct1) regulation during development and maturation of the kidney proximal tubule. *PLoS ONE* 7, E40796
- 80 Harwood, M.D. *et al.* (2012) Absolute abundance and function of intestinal drug transporters: a prerequisite for fully mechanistic in vitro–in vivo extrapolation of oral drug absorption. *Biopharm. Drug Dispos.* <http://dx.doi.org/10.1002/bdd.1810> (Epub ahead of print)
- 81 Iusuf, D. *et al.* (2012) Functions of OATP1A and 1B transporters *in vivo*: insights from mouse models. *Trends Pharmacol. Sci.* 33, 100–108
- 82 Karlgren, M. *et al.* (2012) Classification of inhibitors of hepatic Organic Anion Transporting Polypeptides (OATPs): influence of protein expression on drug–drug interactions. *J. Med. Chem.* 55, 4740–4763
- 83 Kobayashi, H. *et al.* (2012) Human equilibrative nucleoside transporter 1 expression predicts survival of advanced cholangiocarcinoma patients treated with gemcitabine-based adjuvant chemotherapy after surgical resection. *Ann. Surg.* 256, 288–296
- 84 Lai, Y. *et al.* (2012) Impact of drug transporter pharmacogenomics on pharmacokinetic and pharmacodynamic variability – considerations for drug development. *Expert Opin. Drug Metab. Toxicol.* 8, 723–743
- 85 Li, R.W. *et al.* (2012) Physiological and pharmacological roles of vascular nucleoside transporters. *J. Cardiovasc. Pharmacol.* 59, 10–15
- 86 Mandery, K. *et al.* (2012) Interaction of innovative small molecule drugs used for cancer therapy with drug transporters. *Br. J. Pharm.* 165, 345–362
- 87 Morinaga, S. *et al.* (2012) Immunohistochemical analysis of human equilibrative nucleoside transporter-1 (hENT1) predicts survival in resected pancreatic cancer patients treated with adjuvant gemcitabine monotherapy. *Ann. Surg. Oncol.* 19 (Suppl. 3), 558–564
- 88 Mulgaonkar, A. *et al.* (2012) Fluoroquinolone disposition: identification of the contribution of renal secretory and reabsorptive drug transporters. *Expert Opin. Drug Metab. Toxicol.* 8, 553–569
- 89 Murata, Y. *et al.* (2012) Human equilibrative nucleoside transporter 1 expression is a strong independent prognostic factor in UICC T3–T4 pancreatic cancer patients treated with preoperative gemcitabine-based chemoradiotherapy. *J. Hepatobiliary Pancreat. Sci.* 19, 413–425
- 90 Nakanishi, T. and Tamai, I. (2012) Genetic polymorphisms of OATP transporters and their impact on intestinal absorption and hepatic disposition of drugs. *Drug Metab. Pharmacokinet.* 27, 106–121
- 91 Neuvonen, P.J. (2012) Towards safer and more predictable drug treatment – reflections from studies of the first BCPT prize awardee. *Basic Clin. Pharmacol. Toxicol.* 110, 207–218
- 92 Obaidat, A. *et al.* (2012) The expression and function of organic anion transporting polypeptides in normal tissues and in cancer. *Annu. Rev. Pharmacol. Toxicol.* 52, 135–151
- 93 Rostami-Hodjegan, A. (2012) Physiologically based pharmacokinetics joined with *in vitro*–*in vivo* extrapolation of ADME: a marriage under the arch of systems pharmacology. *Clin. Pharmacol. Ther.* 92, 50–61
- 94 Roth, M. *et al.* (2012) OATPs, OATs and OCTs: the organic anion and cation transporters of the SLCO and SLC22A gene superfamilies. *Br. J. Pharmacol.* 165, 1260–1287
- 95 Saadatmand, A.R. *et al.* (2012) The prototypic pharmacogenetic drug debrisoquine is a substrate of the genetically polymorphic organic cation transporter OCT1. *Biochem. Pharmacol.* 83, 1427–1434
- 96 Salomon, J.J. and Ehrhardt, C. (2012) Organic cation transporters in the blood–air barrier: expression and implications for pulmonary drug delivery. *Ther. Deliv.* 3, 735–747
- 97 Sissung, T.M. *et al.* (2012) Transporter pharmacogenetics: transporter polymorphisms affect normal physiology, diseases, and pharmacotherapy. *Discov. Med.* 13, 19–34
- 98 Sprowl, J.A. *et al.* (2012) Contribution of tumoral and host solute carriers to clinical drug response. *Drug Resist. Updat.* 15, 5–20
- 99 Tamai, I. (2012) Oral drug delivery utilizing intestinal OATP transporters. *Adv. Drug Deliv. Rev.* 64, 508–514
- 100 Vadlapudi, A.D. *et al.* (2012) Sodium dependent multivitamin transporter (SMVT): a potential target for drug delivery. *Curr. Drug Targets* 13, 994–1003
- 101 Varma, M.V.S. *et al.* (2012) Physiologically based modeling of pravastatin transporter-mediated hepatobiliary disposition and drug–drug interactions. *Pharm. Res.* 29, 2860–2873
- 102 Yoshida, K. *et al.* (2012) Transporter-mediated drug–drug interactions involving OATP substrates: predictions based on *in vitro* inhibition studies. *Clin. Pharmacol. Ther.* 91, 1053–1064
- 103 Chalmers, A.F. (1999) *What Is This Thing Called Science? An Assessment of the Nature and Status of Science and Its Methods*. Open University Press
- 104 Beck, J.G. *et al.* (2012) Intestinal permeability of cyclic peptides: common key backbone motifs identified. *J. Am. Chem. Soc.* 134, 12125–12133
- 105 Opekarová, M. and Tanner, W. (2003) Specific lipid requirements of membrane proteins – a putative bottleneck in heterologous expression. *Biochim. Biophys. Acta* 1610, 11–22
- 106 Asami, K. (2012) Dielectric spectroscopy reveals nanoholes in erythrocyte ghosts. *Soft Matter* 8, 3250–3257
- 107 Levin, V.A. (1980) Relationship of octanol/water partition coefficient and molecular weight to rat brain capillary permeability. *J. Med. Chem.* 23, 682–684
- 108 Schwan, H.P. (1957) Electrical properties of tissues and cell suspensions. *Adv. Biol. Med. Phys.* 5, 147–209
- 109 Harris, C.M. and Kell, D.B. (1985) On the dielectrically observable consequences of the diffusional motions of lipids and proteins in membranes. 2. Experiments with microbial cells, protoplasts and membrane vesicles. *Eur. Biophys. J.* 13, 11–24
- 110 Harris, C.M. *et al.* (1987) The dielectric permittivity of microbial suspensions at radio frequencies: a novel method for the estimation of microbial biomass. *Enzyme Microb. Technol.* 9, 181–186
- 111 Pethig, R. and Kell, D.B. (1987) The passive electrical properties of biological systems: their significance in physiology, biophysics and biotechnology. *Phys. Med. Biol.* 32, 933–970
- 112 Di Biasio, A. and Cametti, C. (2011) On the dielectric relaxation of biological cell suspensions: the effect of the membrane electrical conductivity. *Colloids Surf. B: Biointerfaces* 84, 433–441
- 113 Raychaudhuri, P. *et al.* (2011) Fluorinated amphiphiles control the insertion of alpha-hemolysin pores into lipid bilayers. *Biochemistry* 50, 1599–1606
- 114 Rincon-Restrepo, M. *et al.* (2011) Controlled translocation of individual DNA molecules through protein nanopores with engineered molecular brakes. *Nano Lett.* 11, 746–750
- 115 Agre, P. *et al.* (2002) Aquaporin water channels – from atomic structure to clinical medicine. *J. Physiol.* 542 (Pt 1), 3–16
- 116 Morishita, Y. *et al.* (2004) Molecular mechanisms and drug development in aquaporin water channel diseases: aquaporin superfamily (superaquaporins): expansion of aquaporins restricted to multicellular organisms. *J. Pharmacol. Sci.* 96, 276–279
- 117 Fujimoto, N. *et al.* (2006) Glycerol uptake in HCT-15 human colon cancer cell line by Na⁺-dependent carrier-mediated transport. *Biol. Pharm. Bull.* 29, 150–154
- 118 Hara-Chikuma, M. and Verkman, A.S. (2005) Aquaporin-3 functions as a glycerol transporter in mammalian skin. *Biol. Cell* 97, 479–486
- 119 Ohgusu, Y. *et al.* (2008) Functional characterization of human aquaporin 9 as a facilitative glycerol carrier. *Drug Metab. Pharmacokinet.* 23, 279–284
- 120 Ishibashi, K. *et al.* (2011) The evolutionary aspects of aquaporin family. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 300, R566–R576

- 121 Ishii, M. *et al.* (2011) Dual functional characteristic of human aquaporin 10 for solute transport. *Cell. Physiol. Biochem.* 27, 749–756
- 122 Bagnasco, S.M. (2005) Role and regulation of urea transporters. *Pflugers Arch.* 450, 217–226
- 123 Bagnasco, S.M. (2006) The erythrocyte urea transporter UT-B. *J. Membr. Biol.* 212, 133–138
- 124 Smith, C.P. (2009) Mammalian urea transporters. *Exp. Physiol.* 94, 180–185
- 125 Stewart, G. (2011) The emerging physiological roles of the SLC14A family of urea transporters. *Br. J. Pharmacol.* 164, 1780–1792
- 126 Walker, A.L. *et al.* (2011) Transcellular movement of hydroxyurea is mediated by specific solute carrier transporters. *Exp. Hematol.* 39, 446–456
- 127 Weiner, I.D. and Hamm, L.L. (2007) Molecular mechanisms of renal ammonia transport. *Annu. Rev. Physiol.* 69, 317–340
- 128 Lamoureux, G. *et al.* (2010) Transport mechanisms in the ammonium transporter family. *Transfus. Clin. Biol.* 17, 168–175
- 129 Nakhoul, N.L. *et al.* (2010) Substrate specificity of Rhbg: ammonium and methyl ammonium transport. *Am. J. Physiol. Cell Physiol.* 299, C695–C705
- 130 Wagner, C.A. *et al.* (2011) The rhesus protein RhCG: a new perspective in ammonium transport and distal urinary acidification. *Kidney Int.* 79, 154–161
- 131 Weiner, I.D. and Verlander, J.W. (2011) Role of NH₃ and NH₄⁺ transporters in renal acid-base transport. *Am. J. Physiol. Renal Physiol.* 300, F11–F23
- 132 Pantoja, O. (2012) High affinity ammonium transporters: molecular mechanism of action. *Front. Plant Sci.* 3, 34
- 133 Romero, M.F. *et al.* (2004) The SLC4 family of HCO₃⁻-transporters. *Pflugers Arch.* 447, 495–509
- 134 Steward, M.C. *et al.* (2005) Mechanisms of bicarbonate secretion in the pancreatic duct. *Annu. Rev. Physiol.* 67, 377–409
- 135 Alper, S.L. (2009) Molecular physiology and genetics of Na⁺-independent SLC4 anion exchangers. *J. Exp. Biol.* 212 (Pt 11), 1672–1683
- 136 Endeward, V. *et al.* (2006) Evidence that aquaporin 1 is a major pathway for CO₂ transport across the human erythrocyte membrane. *FASEB J.* 20, 1974–1981
- 137 Maurel, C. *et al.* (2008) Plant aquaporins: membrane channels with multiple integrated functions. *Annu. Rev. Plant Biol.* 59, 595–624
- 138 Boron, W.F. *et al.* (2011) Intrinsic CO₂ permeability of cell membranes and potential biological relevance of CO₂ channels. *ChemPhysChem* 12, 1017–1019
- 139 Keleti, T. (1986) *Basic Enzyme Kinetics*. Akadémiai Kiadó
- 140 Cornish-Bowden, A. (1995) *Fundamentals of Enzyme Kinetics* (2nd edn), Portland Press
- 141 Fersht, A. (1999) *Structure and Mechanism in Protein Science: A Guide to Enzyme Catalysis and Protein Folding*. W.H. Freeman
- 142 Aharoni, A. *et al.* (2005) The 'evolvability' of promiscuous protein functions. *Nat. Genet.* 37, 73–76
- 143 Nobeli, I. *et al.* (2009) Protein promiscuity and its implications for biotechnology. *Nat. Biotechnol.* 27, 157–167
- 144 Khersonsky, O. and Tawfik, D.S. (2010) Enzyme promiscuity: a mechanistic and evolutionary perspective. *Annu. Rev. Biochem.* 79, 471–505
- 145 Khersonsky, O. and Tawfik, D.S. (2010) Enzyme promiscuity: evolutionary and mechanistic aspects. In *Comprehensive Natural Products II Chemistry and Biology*, (Vol. 8) (Mander, L. and Lui, H.-W., eds) pp. 48–90, Elsevier
- 146 Humble, M.S. and Berglund, P. (2011) Biocatalytic promiscuity. *Eur. J. Org. Chem.* 19, 3391–3401
- 147 Günther, S. *et al.* (2008) SuperTarget and Matador: resources for exploring drug–target relationships. *Nucleic Acids Res.* 36 (Database issue), D919–D922
- 148 Leong, M.K. *et al.* (2009) Development of a new predictive model for interactions with human cytochrome P450 2A6 using pharmacophore ensemble/support vector machine (PhE/SVM) approach. *Pharm. Res.* 26, 987–1000
- 149 Cheng, F. *et al.* (2011) Insights into molecular basis of cytochrome p450 inhibitory promiscuity of compounds. *J. Chem. Inf. Model.* 51, 2482–2495
- 150 Hecker, N. *et al.* (2012) SuperTarget goes quantitative: update on drug–target interactions. *Nucleic Acids Res.* 40 (Database issue), D1113–D1117
- 151 Bencharit, S. *et al.* (2003) Structural basis of heroin and cocaine metabolism by a promiscuous human drug-processing enzyme. *Nat. Struct. Biol.* 10, 349–356
- 152 Hagenbuch, B. and Meier, P.J. (2004) Organic anion transporting polypeptides of the OATP/SLC21 family: phylogenetic classification as OATP/SLCO superfamily, new nomenclature and molecular/functional properties. *Pflugers Arch.* 447, 653–665
- 153 Watanabe, T. *et al.* (2010) Application of physiologically based pharmacokinetic modeling and clearance concept to drugs showing transporter-mediated distribution and clearance in humans. *J. Pharmacokin. Pharmacodyn.* 37, 575–590
- 154 Hagenbuch, B. (2010) Drug uptake systems in liver and kidney: a historic perspective. *Clin. Pharmacol. Ther.* 87, 39–47
- 155 Diao, L. *et al.* (2010) Quantitative structure activity relationship for inhibition of human organic cation/carnitine transporter. *Mol. Pharm.* 7, 2120–2131
- 156 Ciarimboli, G. (2011) Role of organic cation transporters in drug-induced toxicity. *Expert Opin. Drug Metab. Toxicol.* 7, 159–174
- 157 Ekins, S. *et al.* (2012) A substrate pharmacophore for the human organic cation/carnitine transporter identifies compounds associated with rhabdomyolysis. *Mol. Pharm.* 9, 905–913
- 158 Tanihara, Y. *et al.* (2007) Substrate specificity of MATE1 and MATE2-K, human multidrug and toxin extrusions/H(+)-organic cation antiporters. *Biochem. Pharmacol.* 74, 359–371
- 159 Meyer zu Schwabedissen, H.E. *et al.* (2010) Human multidrug and toxin extrusion 1 (MATE1/SLC47A1) transporter: functional characterization, interaction with OCT2 (SLC22A2), and single nucleotide polymorphisms. *Am. J. Physiol. Renal Physiol.* 298, F997–F1005
- 160 Astorga, B. *et al.* (2012) Molecular determinants of ligand selectivity for the human multidrug and toxin extruder proteins MATE1 and MATE2-K. *J. Pharmacol. Exp. Ther.* 341, 743–755
- 161 Ma, Q. and Lu, A.Y. (2008) The challenges of dealing with promiscuous drug-metabolizing enzymes, receptors and transporters. *Curr. Drug Metab.* 9, 374–383
- 162 Aller, S.G. *et al.* (2009) Structure of P-glycoprotein reveals a molecular basis for poly-specific drug binding. *Science* 323, 1718–1722
- 163 Fernandes, J. and Gattass, C.R. (2009) Topological polar surface area defines substrate transport by multidrug resistance associated protein 1 (MRP1/ABCC1). *J. Med. Chem.* 52, 1214–1218
- 164 Marquez, B. and Van Bambeke, F. (2011) ABC multidrug transporters: target for modulation of drug pharmacokinetics and drug–drug interactions. *Curr. Drug Targets* 12, 600–620
- 165 Dharia, N.V. *et al.* (2010) Whole-genome sequencing and microarray analysis of *ex vivo* *Plasmodium vivax* reveal selective pressure on putative drug resistance genes. *Proc. Natl. Acad. Sci. U.S.A.* 107, 20045–20050
- 166 Jovel, I.T. *et al.* (2011) Drug resistance associated genetic polymorphisms in *Plasmodium falciparum* and *Plasmodium vivax* collected in Honduras, Central America. *Malar. J.* 10, 376
- 167 Purkait, B. *et al.* (2012) Mechanism of amphotericin B resistance in clinical isolates of *Leishmania donovani*. *Antimicrob. Agents Chemother.* 56, 1031–1041
- 168 Chopra, I. and Roberts, M. (2001) Tetracycline antibiotics: mode of action, applications, molecular biology, and epidemiology of bacterial resistance. *Microbiol. Mol. Biol. Rev.* 65, 232–260
- 169 Tegos, G. *et al.* (2002) Multidrug pump inhibitors uncover remarkable activity of plant antimicrobials. *Antimicrob. Agents Chemother.* 46, 3133–3141
- 170 Kumar, A. and Schweizer, H.P. (2005) Bacterial resistance to antibiotics: active efflux and reduced uptake. *Adv. Drug Deliv. Rev.* 57, 1486–1513
- 171 Lomovskaya, O. *et al.* (2007) Waltzing transporters and 'the dance macabre' between humans and bacteria. *Nat. Rev. Drug Discov.* 6, 56–65
- 172 Roberts, M.C. (2008) Update on macrolide-lincosamide-streptogramin, ketolide, and oxazolidinone resistance genes. *FEMS Microbiol. Lett.* 282, 147–159
- 173 da Silva, P.E. *et al.* (2011) Efflux as a mechanism for drug resistance in *Mycobacterium tuberculosis*. *FEMS Immunol. Med. Microbiol.* 63, 1–9
- 174 Kitaoka, M. *et al.* (2011) Antibiotic resistance mechanisms of *Vibrio cholerae*. *J. Med. Microbiol.* 60 (Pt 4), 397–407
- 175 Licht, A. and Schneider, E. (2011) ATP binding cassette systems: structures, mechanisms, and functions. *Central Eur. J. Biol.* 6, 785–801
- 176 Poole, K. (2012) Efflux-mediated antimicrobial resistance. In *Antibiotic Discovery and Development* (Dougherty, T.J. and Pucci, M.J., eds), pp. 349–395, Springer
- 177 Prasad, R. and Goffeau, A. (2012) Yeast ATP-binding cassette transporters conferring multidrug resistance. *Annu. Rev. Microbiol.* 66, 39–63
- 178 König, J. *et al.* (2011) Double-transfected MDCK cells expressing human OCT1/MATE1 or OCT2/MATE1: determinants of uptake and transcellular translocation of organic cations. *Br. J. Pharmacol.* 163, 546–555
- 179 Mellors, A. (1976) The Haldane relationship; enzymes and equilibrium. *Biochem. Educ.* 4, 71
- 180 Alberty, R.A. (2006) Relations between biochemical thermodynamics and biochemical kinetics. *Biophys. Chem.* 124, 11–17
- 181 Lanthaler, K. *et al.* (2011) Genome-wide assessment of the carriers involved in the cellular uptake of drugs: a model system in yeast. *BMC Biol.* 9, 70
- 182 Oliver, S.G. *et al.* (1992) The complete DNA sequence of yeast chromosome III. *Nature* 357, 38–46
- 183 Goffeau, A. *et al.* (1996) Life with 6000 genes. *Science* 274, 546–567
- 184 Giaever, G. *et al.* (2002) Functional profiling of the *Saccharomyces cerevisiae* genome. *Nature* 418, 387–391
- 185 Giaever, G. (2003) A chemical genomics approach to understanding drug action. *Trends Pharmacol. Sci.* 24, 444–446
- 186 Delneri, D. *et al.* (2008) Identification and characterization of high-flux-control genes of yeast through competition analyses in continuous cultures. *Nat. Genet.* 40, 113–117

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- 187 Li, Y.B. and Trush, M.A. (1998) Diphenyleioidonium, an NAD(P)H oxidase inhibitor, also potently inhibits mitochondrial reactive oxygen species production. *Biochem. Biophys. Res. Commun.* 253, 295–299
- 188 Kono, H. et al. (2001) Diphenyleioidonium sulfate, an NADPH oxidase inhibitor, prevents early alcohol-induced liver injury in the rat. *Am. J. Physiol.* 280, G1005–G1012
- 189 Fairlamb, A.H. et al. (1989) Trypanothione is the primary target for arsenical drugs against African trypanosomes. *Proc. Natl. Acad. Sci. U.S.A.* 86, 2607–2611
- 190 Alsford, S. et al. (2012) High-throughput decoding of antitrypanosomal drug efficacy and resistance. *Nature* 482, 232–236
- 191 Lanteri, C.A. et al. (2008) The mitochondrion is a site of trypanocidal action of the aromatic diamidine DB75 in bloodstream forms of *Trypanosoma brucei*. *Antimicrob. Agents Chemother.* 52, 875–882
- 192 de Koning, H.P. (2008) Ever-increasing complexities of diamidine and arsenical crossresistance in African trypanosomes. *Trends Parasitol.* 24, 345–349
- 193 Baker, N. et al. (2012) Aquaglyceroporin 2 controls susceptibility to melarsoprol and pentamidine in African trypanosomes. *Proc. Natl. Acad. Sci. U.S.A.*
- 194 Carter, N.S. and Fairlamb, A.H. (1993) Arsenical-resistant trypanosomes lack an unusual adenosine transporter. *Nature* 361, 173–176
- 195 Mäser, P. et al. (1999) A nucleoside transporter from *Trypanosoma brucei* involved in drug resistance. *Science* 285, 242–244
- 196 De Koning, H.P. (2001) Uptake of pentamidine in *Trypanosoma brucei brucei* is mediated by three distinct transporters: implications for cross-resistance with arsenicals. *Mol. Pharmacol.* 59, 586–592
- 197 de Koning, H.P. et al. (2005) Purine and pyrimidine transport in pathogenic protozoa: from biology to therapy. *FEMS Microbiol. Rev.* 29, 987–1020
- 198 Bellofatto, V. (2007) Pyrimidine transport activities in trypanosomes. *Trends Parasitol.* 23, 187–189 discussion 190
- 199 Stewart, M.L. et al. (2010) Multiple genetic mechanisms lead to loss of functional TbAT1 expression in drug-resistant trypanosomes. *Eukaryot. Cell* 9, 336–343
- 200 Barrett, M.P. et al. (2011) Drug resistance in human African trypanosomiasis. *Future Microbiol.* 6, 1037–1047
- 201 Ortiz, D. et al. (2009) Two novel nucleobase/pentamidine transporters from *Trypanosoma brucei*. *Mol. Biochem. Parasitol.* 163, 67–76
- 202 Alibu, V.P. et al. (2006) The role of *Trypanosoma brucei* MRPA in melarsoprol susceptibility. *Mol. Biochem. Parasitol.* 146, 38–44
- 203 Shahi, S.K. et al. (2002) Overexpression of the putative thiol conjugate transporter TbMRPA causes melarsoprol resistance in *Trypanosoma brucei*. *Mol. Microbiol.* 43, 1129–1138
- 204 Pérez-Victoria, F.J. et al. (2003) Functional cloning of the miltefosine transporter. A novel P-type phospholipid translocase from *Leishmania* involved in drug resistance. *J. Biol. Chem.* 278, 49965–49971
- 205 Pérez-Victoria, F.J. et al. (2006) Mechanisms of experimental resistance of *Leishmania* to miltefosine: Implications for clinical use. *Drug Resist. Updat.* 9, 26–39
- 206 Bhattacharjee, H. and Mukhopadhyay, R. (2009) Drug resistance in *Leishmania*. In *Antimicrobial Drug Resistance* (Mayers, D.L., ed.), pp. 575–587, Humana
- 207 Carlton, J.M.R. et al. (2001) Conservation of a novel vacuolar transporter in *Plasmodium* species and its central role in chloroquine resistance of *P. falciparum*. *Curr. Opin. Microbiol.* 4, 415–420
- 208 Martin, R.E. and Kirk, K. (2004) The malaria parasite's chloroquine resistance transporter is a member of the drug/metabolite transporter superfamily. *Mol. Biol. Evol.* 21, 1938–1949
- 209 Hyde, J.E. (2005) Drug-resistant malaria. *Trends Parasitol.* 21, 494–498
- 210 Summers, R.L. and Martin, R.E. (2010) Functional characteristics of the malaria parasite's 'chloroquine resistance transporter': implications for chemotherapy. *Virulence* 1, 304–308
- 211 Roepe, P.D. (2011) PfCRT-mediated drug transport in malarial parasites. *Biochemistry* 50, 163–171
- 212 Sá, J.M. et al. (2011) Malaria drug resistance: new observations and developments. *Essays Biochem.* 51, 137–160
- 213 Papakrivov, J. et al. (2012) Functional characterization of the *Plasmodium falciparum* chloroquine-resistance transporter (PfCRT) in transformed *Dictyostelium discoideum* vesicles. *PLoS ONE* 7, E39569
- 214 Summers, R.L. et al. (2012) Know your enemy: understanding the role of PfCRT in drug resistance could lead to new antimalarial tactics. *Cell. Mol. Life Sci.* 69, 1967–1995
- 215 Alsford, S. et al. (2011) High-throughput phenotyping using parallel sequencing of RNA interference targets in the African trypanosome. *Genome Res.* 21, 915–924
- 216 Baker, N. et al. (2011) Genome-wide RNAi screens in African trypanosomes identify the nifurtimox activator NTR and the eflornithine transporter AAT6. *Mol. Biochem. Parasitol.* 176, 55–57
- 217 Kolev, N.G. et al. (2011) RNA interference in protozoan parasites: achievements and challenges. *Eukaryot. Cell* 10, 1156–1163
- 218 Schumann Burkard, G. et al. (2011) Genome-wide RNAi screens in bloodstream form trypanosomes identify drug transporters. *Mol. Biochem. Parasitol.* 175, 91–94
- 219 Mohr, S.E. and Perrimon, N. (2012) RNAi screening: new approaches, understandings, and organisms. *Wiley Interdiscip. Rev. RNA* 3, 145–158
- 220 Hediger, M.A. et al. (2004) The ABCs of solute carriers: physiological, pathological and therapeutic implications of human membrane transport proteins. Introduction. *Pflügers Arch.* 447, 465–468
- 221 Fredriksson, R. et al. (2008) The solute carrier (SLC) complement of the human genome: phylogenetic classification reveals four major families. *FEBS Lett.* 582, 3811–3816
- 222 Schlessinger, A. et al. (2011) Structure-based discovery of prescription drugs that interact with the norepinephrine transporter, NET. *Proc. Natl. Acad. Sci. U.S.A.* 108, 15810–15815
- 223 Sai, Y. (2005) Biochemical and molecular pharmacological aspects of transporters as determinants of drug disposition. *Drug Metab. Pharmacokinet.* 20, 91–99
- 224 Xia, C.Q. et al. (2007) Evaluation of drug–transporter interactions using *in vitro* and *in vivo* models. *Curr. Drug Metab.* 8, 341–363
- 225 Masereeuw, R. and Russel, F.G. (2010) Therapeutic implications of renal anionic drug transporters. *Pharmacol. Ther.* 126, 200–216
- 226 Attwood, T.K. et al. (2009) Calling International Rescue: knowledge lost in literature and data landslide! *Biochem. J.* 424, 317–333
- 227 Ideker, T. et al. (2001) A new approach to decoding life: systems biology. *Annu. Rev. Genomics Hum. Genet.* 2, 343–372
- 228 Kitano, H. (2002) Systems biology: a brief overview. *Science* 295, 1662–1664
- 229 Kitano, H. (2002) Computational systems biology. *Nature* 420, 206–210
- 230 Hood, L. (2003) Systems biology: integrating technology, biology, and computation. *Mech. Ageing Dev.* 124, 9–16
- 231 Westerhoff, H.V. and Palsson, B.Ø. (2004) The evolution of molecular biology into systems biology. *Nat. Biotechnol.* 22, 1249–1252
- 232 Klipp, E. et al. (2005) *Systems Biology in Practice: Concepts, Implementation and Clinical Application*. Wiley/VCH
- 233 Alon, U. (2006) *An Introduction to Systems Biology: Design Principles of Biological Circuits*. Chapman and Hall/CRC
- 234 Kell, D.B. (2006) Metabolomics, modelling and machine learning in systems biology: towards an understanding of the languages of cells. The 2005 Theodor Büber lecture. *FEBS J.* 273, 873–894
- 235 Kell, D.B. (2006) Systems biology, metabolic modelling and metabolomics in drug discovery and development. *Drug Discov. Today* 11, 1085–1092
- 236 Palsson, B.Ø. (2006) *Systems Biology: Properties of Reconstructed Networks*. Cambridge University Press
- 237 Duarte, N.C. et al. (2007) Global reconstruction of the human metabolic network based on genomic and bibliomic data. *Proc. Natl. Acad. Sci. U.S.A.* 104, 1777–1782
- 238 Kell, D.B. (2007) The virtual human: towards a global systems biology of multiscale, distributed biochemical network models. *IUBMB Life* 59, 689–695
- 239 Ma, H. et al. (2007) The Edinburgh human metabolic network reconstruction and its functional analysis. *Mol. Syst. Biol.* 3, 135
- 240 Herrgård, M.J. et al. (2008) A consensus yeast metabolic network obtained from a community approach to systems biology. *Nat. Biotechnol.* 26, 1155–1160
- 241 Thiele, I. and Palsson, B.Ø. (2010) Reconstruction annotation jamborees: a community approach to systems biology. *Mol. Syst. Biol.* 6, 361
- 242 Lee, J.W. et al. (2011) Systems metabolic engineering for chemicals and materials. *Trends Biotechnol.* 29, 370–378
- 243 Swainston, N. et al. (2011) The SuBliMinaL Toolbox: automating steps in the reconstruction of metabolic networks. *Integrative Bioinf.* 8, 186
- 244 Smallbone, K. et al. (2007) Something from nothing: bridging the gap between constraint-based and kinetic modelling. *FEBS J.* 274, 5576–5585
- 245 Schellenberger, J. et al. (2011) Quantitative prediction of cellular metabolism with constraint-based models: the COBRA Toolbox v2.0. *Nat. Protoc.* 6, 1290–1307
- 246 Ihekwaba, A.E.C. et al. (2004) Sensitivity analysis of parameters controlling oscillatory signalling in the NF- κ B pathway: the roles of IKK and I κ B α . *Syst. Biol.* 1, 93–103
- 247 Kell, D.B. and Knowles, J.D. (2006) The role of modeling in systems biology. In *System Modeling in Cellular Biology: From Concepts to Nuts and Bolts* (Szallasi, Z. et al. eds), pp. 3–18, MIT Press
- 248 Saltelli, A. et al. (2008) *Global Sensitivity Analysis: The Primer*. Wiley–Blackwell
- 249 Yue, H. et al. (2008) Sensitivity analysis and robust experimental design of a signal transduction pathway system. *Int. J. Chem. Kinet.* 40, 730–741
- 250 Jayawardhana, B. et al. (2008) Bayesian inference of the sites of perturbations in metabolic pathways via Markov Chain Monte Carlo. *Bioinformatics* 24, 1191–1197
- 251 Vyshemirsky, V. and Girolami, M.A. (2008) Bayesian ranking of biochemical system models. *Bioinformatics* 24, 833–839

- 252 Wilkinson, S.J. *et al.* (2008) Proximate parameter tuning for biochemical networks with uncertain kinetic parameters. *Mol. Biosyst.* 4, 74–97
- 253 Sun, D. *et al.* (2002) Comparison of human duodenum and Caco-2 gene expression profiles for 12,000 gene sequences tags and correlation with permeability of 26 drugs. *Pharm. Res.* 19, 1400–1416
- 254 Anderle, P. *et al.* (2004) Intestinal membrane transport of drugs and nutrients: genomics of membrane transporters using expression microarrays. *Eur. J. Pharm. Sci.* 21, 17–24
- 255 Landowski, C.P. *et al.* (2004) Transporter and ion channel gene expression after Caco-2 cell differentiation using 2 different microarray technologies. *AAPS J.* 6, E21
- 256 Pshezhetsky, A.V. *et al.* (2007) Subcellular proteomics of cell differentiation: quantitative analysis of the plasma membrane proteome of Caco-2 cells. *Proteomics* 7, 2201–2215
- 257 Hayashi, R. *et al.* (2008) Comparison of drug transporter gene expression and functionality in Caco-2 cells from 10 different laboratories. *Eur. J. Pharm. Sci.* 35, 383–396
- 258 Ahlin, G. *et al.* (2009) Endogenous gene and protein expression of drug-transporting proteins in cell lines routinely used in drug discovery programs. *Drug Metab. Dispos.* 37, 2275–2283
- 259 Chen, Y.S. *et al.* (2010) Proteomic profiling of MDCK plasma membranes reveals Wnt-5a involvement during oncogenic H-Ras/TGF- β -mediated epithelial-mesenchymal transition. *Mol. Cell. Proteomics* 10 M110.001131
- 260 Pottiez, G. *et al.* (2009) Understanding the blood–brain barrier using gene and protein expression profiling technologies. *Brain Res. Rev.* 62, 83–98
- 261 Hilgendorf, C. *et al.* (2007) Expression of thirty-six drug transporter genes in human intestine, liver, kidney, and organotypic cell lines. *Drug Metab. Dispos.* 35, 1333–1340
- 262 Lepist, E.I. and Ray, A.S. (2012) Renal drug–drug interactions: what we have learned and where we are going. *Expert Opin. Drug Metab. Toxicol.* 8, 433–448
- 263 Okabe, M. *et al.* (2008) Profiling SLCO and SLC22 genes in the NCI-60 cancer cell lines to identify drug uptake transporters. *Mol. Cancer Ther.* 7, 3081–3091
- 264 Kell, D.B. *et al.* (2001) Genomic computing: explanatory analysis of plant expression profiling data using machine learning. *Plant Physiol.* 126, 943–951
- 265 Dumaual, C. *et al.* (2007) Comprehensive assessment of metabolic enzyme and transporter genes using the Affymetrix Targeted Genotyping System. *Pharmacogenomics* 8, 293–305
- 266 Sissung, T.M. *et al.* (2010) Clinical pharmacology and pharmacogenetics in a genomics era: the DMET platform. *Pharmacogenomics* 11, 89–103
- 267 Schiess, R. *et al.* (2009) Analysis of cell surface proteome changes via label-free, quantitative mass spectrometry. *Mol. Cell. Proteom.: MCP* 8, 624–638
- 268 Hofmann, A. *et al.* (2010) Proteomic cell surface phenotyping of differentiating acute myeloid leukemia cells. *Blood* 116, E26–E34
- 269 Frei, A.P. *et al.* (2012) Direct identification of ligand–receptor interactions on living cells and tissues. *Nat. Biotechnol.* 30, 997–1001
- 270 Uhlén, M. *et al.* (2010) Towards a knowledge-based Human Protein Atlas. *Nat. Biotechnol.* 28, 1248–1250
- 271 Lundberg, E. and Uhlén, M. (2010) Creation of an antibody-based subcellular protein atlas. *Proteomics* 10, 3984–3996
- 272 Ioannidis, J.P.A. (2005) Why most published research findings are false. *PLoS Med.* 2, E124
- 273 Broadhurst, D. and Kell, D.B. (2006) Statistical strategies for avoiding false discoveries in metabolomics and related experiments. *Metabolomics* 2, 171–196
- 274 Bakos, E. *et al.* (2000) Interactions of the human multidrug resistance proteins MRP1 and MRP2 with organic anions. *Mol. Pharmacol.* 57, 760–768
- 275 Uwai, Y. *et al.* (2000) Interaction and transport of thiazide diuretics, loop diuretics, and acetazolamide via rat renal organic anion transporter rOAT1. *J. Pharmacol. Exp. Ther.* 295, 261–265
- 276 Race, J.E. *et al.* (1999) Molecular cloning and characterization of two novel human renal organic anion transporters (hOAT1 and hOAT3). *Biochem. Biophys. Res. Commun.* 255, 508–514
- 277 Hasannejad, H. *et al.* (2004) Interactions of human organic anion transporters with diuretics. *J. Pharmacol. Exp. Ther.* 308, 1021–1029
- 278 Eraly, S.A. *et al.* (2006) Decreased renal organic anion secretion and plasma accumulation of endogenous organic anions in OAT1 knock-out mice. *J. Biol. Chem.* 281, 5072–5083
- 279 Vallon, V. *et al.* (2008) Overlapping *in vitro* and *in vivo* specificities of the organic anion transporters OAT1 and OAT3 for loop and thiazide diuretics. *Am. J. Physiol. Renal Physiol.* 294, F867–F873
- 280 Han, Y.F. *et al.* (2011) Association of intergenic polymorphism of organic anion transporter 1 and 3 genes with hypertension and blood pressure response to hydrochlorothiazide. *Am. J. Hypertens.* 24, 340–346
- 281 Bagwell, E.E. *et al.* (1989) Stereoselective uptake of atenolol into storage granules isolated from PC12 cells. *J. Pharmacol. Exp. Ther.* 249, 476–482
- 282 Takara, K. *et al.* (2002) Interaction of digoxin with antihypertensive drugs via MDR1. *Life Sci.* 70, 1491–1500
- 283 Neuhoﬀ, S. *et al.* (2003) pH-dependent bidirectional transport of weakly basic drugs across Caco-2 monolayers: implications for drug–drug interactions. *Pharm. Res.* 20, 1141–1148
- 284 Kato, Y. *et al.* (2009) Involvement of influx and efflux transport systems in gastrointestinal absorption of celi-prolol. *J. Pharm. Sci.* 98, 2529–2539
- 285 Collett, A. *et al.* (1999) Modulation of the permeability of H2 receptor antagonists cimetidine and ranitidine by P-glycoprotein in rat intestine and the human colonic cell line Caco-2. *J. Pharmacol. Exp. Ther.* 288, 171–178
- 286 Gründemann, D. *et al.* (1999) Selective substrates for non-neuronal monoamine transporters. *Mol. Pharmacol.* 56, 1–10
- 287 Cha, S.H. *et al.* (2001) Identification and characterization of human organic anion transporter 3 expressing predominantly in the kidney. *Mol. Pharmacol.* 59, 1277–1286
- 288 Wang, D.S. *et al.* (2002) Involvement of organic cation transporter 1 in hepatic and intestinal distribution of metformin. *J. Pharmacol. Exp. Ther.* 302, 510–515
- 289 Burckhardt, B.C. *et al.* (2003) Transport of cimetidine by flounder and human renal organic anion transporter 1. *Am. J. Physiol. Renal Physiol.* 284, F503–F509
- 290 Motohashi, H. *et al.* (2004) Different transport properties between famotidine and cimetidine by human renal organic ion transporters (SLC22A). *Eur. J. Pharmacol.* 503, 25–30
- 291 Pavek, P. *et al.* (2005) Human breast cancer resistance protein: interactions with steroid drugs, hormones, the dietary carcinogen 2-amino-1-methyl-6-phenylimidazo(4,5-b)pyridine, and transport of cimetidine. *J. Pharmacol. Exp. Ther.* 312, 144–152
- 292 Lash, L.H. *et al.* (2006) Membrane transport function in primary cultures of human proximal tubular cells. *Toxicology* 228, 200–218
- 293 Umehara, K.I. *et al.* (2008) Effect of cationic drugs on the transporting activity of human and rat OCT/Oct 1–3 *in vitro* and implications for drug–drug interactions. *Xenobiotica* 38, 1203–1218
- 294 Kido, Y. *et al.* (2011) Profiling of a prescription drug library for potential renal drug–drug interactions mediated by the organic cation transporter 2. *J. Med. Chem.* 54, 4548–4558
- 295 Thwaites, D.T. *et al.* (1993) Transepithelial glycylsarcosine transport in intestinal Caco-2 cells mediated by expression of H(+)-coupled carriers at both apical and basal membranes. *J. Biol. Chem.* 268, 7640–7642
- 296 Grès, M.C. *et al.* (1998) Correlation between oral drug absorption in humans, and apparent drug permeability in TC-7 cells, a human epithelial intestinal cell line: comparison with the parental Caco-2 cell line. *Pharm. Res.* 15, 726–733
- 297 Faassen, F. *et al.* (2003) Caco-2 permeability, P-glycoprotein transport ratios and brain penetration of heterocyclic drugs. *Int. J. Pharm.* 263, 113–122
- 298 Döppenschmitt, S. *et al.* (1999) Characterization of binding properties to human P-glycoprotein: development of a [³H]verapamil radioligand-binding assay. *J. Pharmacol. Exp. Ther.* 288, 348–357
- 299 Dudley, A.J. *et al.* (2000) The organic cation transporter OCT2 mediates the uptake of beta-adrenoceptor antagonists across the apical membrane of renal LLC-PK(1) cell monolayers. *Br. J. Pharmacol.* 131, 71–79
- 300 Yamakawa, Y. *et al.* (2012) Pharmacophore modeling for hERG channel facilitation. *Biochem. Biophys. Res. Commun.* 418, 161–166
- 301 Yang, J.J. *et al.* (2000) Role of P-glycoprotein in restricting propranolol transport in cultured rabbit conjunctival epithelial cell layers. *Pharm. Res.* 17, 533–538
- 302 D'Emanuele, A. *et al.* (2004) The use of a dendrimer-propranolol prodrug to bypass efflux transporters and enhance oral bioavailability. *J. Control. Release* 95, 447–453
- 303 Zolk, O. *et al.* (2009) Functional characterization of the human organic cation transporter 2 variant p.270AlaSer. *Drug Metab. Dispos.* 37, 1312–1318
- 304 Wang, Y. *et al.* (2010) Stereoselective transport and uptake of propranolol across human intestinal Caco-2 cell monolayers. *Chirality* 22, 361–368
- 305 Kekuda, R. *et al.* (1998) Cloning and functional characterization of a potential-sensitive, polyspecific organic cation transporter (OCT3) most abundantly expressed in placenta. *J. Biol. Chem.* 273, 15971–15979
- 306 Wu, X. *et al.* (2000) Structural and functional characteristics and tissue distribution pattern of rat OCTN1, an organic cation transporter, cloned from placenta. *Biochim. Biophys. Acta* 1466, 315–327
- 307 O'Brien, F. *et al.* (2012) Inhibition of P-glycoprotein enhances transport of imipramine across the blood–brain barrier: microdialysis studies in conscious freely moving rats. *Br. J. Pharmacol.* 166, 1333–1343
- 308 Apiwattanakul, N. *et al.* (1999) Transport properties of nonsteroidal anti-inflammatory drugs by organic anion transporter 1 expressed in *Xenopus laevis* oocytes. *Mol. Pharmacol.* 55, 847–854

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- 309 Tsuda, M. *et al.* (1999) Transport of ochratoxin A by renal multispecific organic anion transporter 1. *J. Pharmacol. Exp. Ther.* 289, 1301–1305
- 310 Jung, K.Y. *et al.* (2001) Characterization of ochratoxin A transport by human organic anion transporters. *Life Sci.* 69, 2123–2135
- 311 Babu, E. *et al.* (2002) Role of human organic anion transporter 4 in the transport of ochratoxin A. *Biochim. Biophys. Acta* 1590, 64–75
- 312 Khamdang, S. *et al.* (2002) Interactions of human organic anion transporters and human organic cation transporters with nonsteroidal anti-inflammatory drugs. *J. Pharmacol. Exp. Ther.* 303, 534–539
- 313 Takeda, M. *et al.* (2002) Characterization of methotrexate transport and its drug interactions with human organic anion transporters. *J. Pharmacol. Exp. Ther.* 302, 666–671
- 314 El-Sheikh, A.A. *et al.* (2007) Interaction of nonsteroidal anti-inflammatory drugs with multidrug resistance protein (MRP) 2/ABCC2- and MRP4/ABCC4-mediated methotrexate transport. *J. Pharmacol. Exp. Ther.* 320, 229–235
- 315 El-Sheikh, A.A. *et al.* (2008) Mechanisms of renal anionic drug transport. *Eur. J. Pharmacol.* 585, 245–255
- 316 Mulato, A.S. *et al.* (2000) Nonsteroidal anti-inflammatory drugs efficiently reduce the transport and cytotoxicity of adefovir mediated by the human renal organic anion transporter 1. *J. Pharmacol. Exp. Ther.* 295, 10–15
- 317 Morita, N. *et al.* (2005) Functional involvement of rat organic anion transporter 2 (Slc22a7) in the hepatic uptake of the nonsteroidal anti-inflammatory drug ketoprofen. *Drug Metab. Dispos.* 33, 1151–1157
- 318 Cui, D. and Morris, M.E. (2009) The drug of abuse gamma-hydroxybutyrate is a substrate for sodium-coupled monocarboxylate transporter (SMCT) 1 (SLC5A8): characterization of SMCT-mediated uptake and inhibition. *Drug Metab. Dispos.* 37, 1404–1410
- 319 Shitara, Y. *et al.* (2002) Comparative inhibitory effects of different compounds on rat oatpl (slc21a1)- and Oatp2 (Slc21a5)-mediated transport. *Pharm. Res.* 19, 147–153
- 320 Williams, A.J. (2008) Internet-based tools for communication and collaboration in chemistry. *Drug Discov. Today* 13, 502–506
- 321 Williams, A.J. (2008) A perspective of publicly accessible/open-access chemistry databases. *Drug Discov. Today* 13, 495–501
- 322 Gaulton, A. and Overington, J.P. (2010) Role of open chemical data in aiding drug discovery and design. *Future Med. Chem.* 2, 903–907
- 323 Tsinman, O. *et al.* (2011) Physicochemical selectivity of the BBB microenvironment governing passive diffusion – matching with a porcine brain lipid extract artificial membrane permeability model. *Pharm. Res.* 28, 337–363
- 324 Rolfsson, O. *et al.* (2011) The human metabolic reconstruction Recon 1 directs hypotheses of novel human metabolic functions. *BMC Syst. Biol.* 5, 155
- 325 Shlomi, T. *et al.* (2008) Network-based prediction of human tissue-specific metabolism. *Nat. Biotechnol.* 26, 1003–1010
- 326 Hao, T. *et al.* (2012) The reconstruction and analysis of tissue specific human metabolic networks. *Mol. Biosyst.* 8, 663–670
- 327 Pardridge, W.M. (2006) Molecular Trojan horses for blood–brain barrier drug delivery. *Curr. Opin. Pharmacol.* 6, 494–500
- 328 Jeffrey, P. and Summerfield, S.G. (2007) Challenges for blood–brain barrier (BBB) screening. *Xenobiotica* 37, 1135–1151
- 329 Pardridge, W.M. (2007) Blood–brain barrier delivery. *Drug Discov. Today* 12, 54–61
- 330 Pavan, B. *et al.* (2008) Progress in drug delivery to the central nervous system by the prodrug approach. *Molecules* 13, 1035–1065
- 331 Bernacki, J. *et al.* (2008) Physiology and pharmacological role of the blood–brain barrier. *Pharmacol. Rep.* 60, 600–622
- 332 Neuwelt, E. *et al.* (2008) Strategies to advance translational research into brain barriers. *Lancet Neurol.* 7, 84–96
- 333 Eyal, S. *et al.* (2009) Drug interactions at the blood–brain barrier: fact or fantasy? *Pharmacol. Ther.* 123, 80–104
- 334 Varatharajan, L. and Thomas, S.A. (2009) The transport of anti-HIV drugs across blood–CNS interfaces: summary of current knowledge and recommendations for further research. *Antiviral Res.* 82, A99–A109
- 335 Abbott, N.J. *et al.* (2010) Structure and function of the blood–brain barrier. *Neurobiol. Dis.* 37, 13–25
- 336 Cardoso, F.L. *et al.* (2010) Looking at the blood–brain barrier: molecular anatomy and possible investigation approaches. *Brain Res. Rev.* 64, 328–363
- 337 Pavan, B. and Dalpiaz, A. (2011) Prodrugs and endogenous transporters: are they suitable tools for drug targeting into the central nervous system? *Curr. Pharm. Des.* 17, 3560–3576
- 338 Banks, W.A. (2012) Drug delivery to the brain in Alzheimer's disease: consideration of the blood–brain barrier. *Adv. Drug Deliv. Rev.* 64, 629–639
- 339 Broccatelli, F. *et al.* (2012) Improving the prediction of the brain disposition for orally administered drugs using BDDCS. *Adv. Drug Deliv. Rev.* 64, 95–109
- 340 Chen, Y. and Liu, L. (2012) Modern methods for delivery of drugs across the blood–brain barrier. *Adv. Drug Deliv. Rev.* 64, 640–665
- 341 Geldenhuys, W.J. *et al.* (2012) Novel models for assessing blood–brain barrier drug permeation. *Expert Opin. Drug Metab. Toxicol.* 8, 647–653
- 342 Löscher, W. and Potschka, H. (2005) Role of drug efflux transporters in the brain for drug disposition and treatment of brain diseases. *Prog. Neurobiol.* 76, 22–76
- 343 Shen, S. and Zhang, W. (2010) ABC transporters and drug efflux at the blood–brain barrier. *Rev. Neurosci.* 21, 29–53
- 344 Tsuji, A. (2005) Small molecular drug transfer across the blood–brain barrier via carrier-mediated transport systems. *NeuroRx* 2, 54–62
- 345 Gabathuler, R. (2009) Blood–brain barrier transport of drugs for the treatment of brain diseases. *CNS Neurol. Disord. Drug Targets* 8, 195–204
- 346 Urquhart, B.L. and Kim, R.B. (2009) Blood–brain barrier transporters and response to CNS-active drugs. *Eur. J. Clin. Pharmacol.* 65, 1063–1070
- 347 Gabathuler, R. (2010) Approaches to transport therapeutic drugs across the blood–brain barrier to treat brain diseases. *Neurobiol. Dis.* 37, 48–57
- 348 Ueno, M. *et al.* (2010) Transporters in the brain endothelial barrier. *Curr. Med. Chem.* 17, 1125–1138
- 349 Chang, C. *et al.* (2006) Pharmacophore-based discovery of ligands for drug transporters. *Adv. Drug Deliv. Rev.* 58, 1431–1450
- 350 Ohtsuki, S. and Terasaki, T. (2007) Contribution of carrier-mediated transport systems to the blood–brain barrier as a supporting and protecting interface for the brain: importance for CNS drug discovery and development. *Pharm. Res.* 24, 1745–1758
- 351 Rautio, J. *et al.* (2008) Prodrug approaches for CNS delivery. *AAPS J.* 10, 92–102
- 352 Patel, M.M. *et al.* (2009) Getting into the brain: approaches to enhance brain drug delivery. *CNS Drugs* 23, 35–58
- 353 Gynther, M. *et al.* (2008) Large neutral amino acid transporter enables brain drug delivery via prodrugs. *J. Med. Chem.* 51, 932–936
- 354 Gynther, M. *et al.* (2009) Glucose promoiety enables glucose transporter mediated brain uptake of ketoprofen and indomethacin prodrugs in rats. *J. Med. Chem.* 52, 3348–3353
- 355 Gynther, M. *et al.* (2010) Brain uptake of ketoprofen–lysine prodrug in rats. *Int. J. Pharm.* 399, 121–128
- 356 Peura, L. *et al.* (2011) Large amino acid transporter 1 (LAT1) prodrugs of valproic acid: new prodrug design ideas for central nervous system delivery. *Mol. Pharm.* 8, 1857–1866
- 357 Kooijmans, S.A. *et al.* (2012) The involvement of a Na⁺- and Cl⁻-dependent transporter in the brain uptake of amantadine and rimantadine. *Mol. Pharm.* 9, 883–893
- 358 Dalpiaz, A. *et al.* (2007) Molecular mechanism involved in the transport of a prodrug dopamine glycosyl conjugate. *Int. J. Pharm.* 336, 133–139
- 359 Fan, W. *et al.* (2011) Design, synthesis and biological evaluation of brain-specific glucosyl thiamine disulfide prodrugs of naproxen. *Eur. J. Med. Chem.* 46, 3651–3661
- 360 Mahmoud, S. and Mohammad, A. (2010) Brain-specific delivery of naproxen using different carrier systems. *Arch. Pharm. (Weinheim)* 343, 639–647
- 361 Diao, L. and Polli, J.E. (2011) Synthesis and *in vitro* characterization of drug conjugates of L-carnitine as potential prodrugs that target human OCTN2. *J. Pharm. Sci.* 100, 3802–3816
- 362 Dickens, D. *et al.* (2012) Lamotrigine is a substrate for OCT1 in brain endothelial cells. *Biochem. Pharmacol.* 83, 805–814
- 363 Cheng, Z. *et al.* (2012) Hydrophilic anti-migraine triptans are substrates for OATP1A2, a transporter expressed at human blood–brain barrier. *Xenobiotica* 42, 880–890
- 364 Lockman, P.R. *et al.* (2008) Carrier-mediated transport of the quaternary ammonium neuronal nicotinic receptor antagonist n,n'-dodecylbispicolinium dibromide at the blood–brain barrier. *J. Pharmacol. Exp. Ther.* 324, 244–250
- 365 Geldenhuys, W.J. *et al.* (2010) Predictive screening model for potential vector-mediated transport of cationic substrates at the blood–brain barrier choline transporter. *Bioorg. Med. Chem. Lett.* 20, 870–877
- 366 Geldenhuys, W.J. and Allen, D.D. (2012) The blood–brain barrier choline transporter. *Central Nerv. Syst. Agents Med. Chem.*
- 367 Okura, T. *et al.* (2011) Functional characterization of rat plasma membrane monoamine transporter in the blood–brain and blood–cerebrospinal fluid barriers. *J. Pharm. Sci.* 100, 3924–3938
- 368 Sadiq, M.W. *et al.* (2011) Diphenhydramine active uptake at the blood–brain barrier and its interaction with oxycodone *in vitro* and *in vivo*. *J. Pharm. Sci.* 100, 3912–3923
- 369 Daneman, R. *et al.* (2010) The mouse blood–brain barrier transcriptome: a new resource for understanding the development and function of brain endothelial cells. *PLoS ONE* 5, E13741

- 370 Krejsa, C.M. *et al.* (2003) Predicting ADME properties and side effects: The BioPrint approach. *Curr. Opin. Drug Discov. Dev.* 6, 470–480
- 371 Ekins, S. (2004) Predicting undesirable drug interactions with promiscuous proteins *in silico*. *Drug Discov. Today* 9, 276–285
- 372 Roth, B.L. *et al.* (2004) Magic shotguns versus magic bullets: selectively non-selective drugs for mood disorders and schizophrenia. *Nat. Rev. Drug Discov.* 3, 353–359
- 373 Fliri, A.F. *et al.* (2005) Analysis of drug-induced effect patterns to link structure and side effects of medicines. *Nat. Chem. Biol.* 1, 389–397
- 374 Hopkins, A.L. *et al.* (2006) Can we rationally design promiscuous drugs? *Curr. Opin. Struct. Biol.* 16, 127–136
- 375 Li, H. *et al.* (2006) TarFisDock: a web server for identifying drug targets with docking approach. *Nucleic Acids Res.* 34 (Web Server issue), W219–W224
- 376 Paolini, G.V. *et al.* (2006) Global mapping of pharmacological space. *Nat. Biotechnol.* 24, 805–815
- 377 Azaoui, K. *et al.* (2007) Modeling promiscuity based on *in vitro* safety pharmacology profiling data. *ChemMedChem* 2, 874–880
- 378 Keiser, M.J. *et al.* (2007) Relating protein pharmacology by ligand chemistry. *Nat. Biotechnol.* 25, 197–206
- 379 Yildirim, M.A. *et al.* (2007) Drug–target network. *Nat. Biotechnol.* 25, 1119–1126
- 380 Campillos, M. *et al.* (2008) Drug–target identification using side-effect similarity. *Science* 321, 263–266
- 381 Keiser, M.J. *et al.* (2009) Predicting new molecular targets for known drugs. *Nature* 462, 175–181
- 382 Keiser, M.J. and Hert, J. (2009) Off-target networks derived from ligand set similarity. *Methods Mol. Biol.* 575, 195–205
- 383 Park, K. *et al.* (2009) Predicting the multi-modal binding propensity of small molecules: towards an understanding of drug promiscuity. *Mol. Biosyst.* 5, 844–853
- 384 Bantscheff, M. *et al.* (2009) Revealing promiscuous drug–target interactions by chemical proteomics. *Drug Discov. Today* 14, 1021–1029
- 385 Hopkins, A.L. (2009) Predicting promiscuity. *Nature* 462, 167–168
- 386 Mestres, J. and Gregori-Puigjané, E. (2009) Conciliating binding efficiency and polypharmacology. *Trends Pharmacol. Sci.* 30, 470–474
- 387 Peters, J.U. *et al.* (2009) Pharmacological promiscuity: dependence on compound properties and target specificity in a set of recent Roche compounds. *ChemMedChem* 4, 680–686
- 388 Garcia-Serna, R. and Mestres, J. (2010) Anticipating drug side effects by comparative pharmacology. *Expert Opin. Drug Metab. Toxicol.* 6, 1253–1263
- 389 Keiser, M.J. *et al.* (2010) The chemical basis of pharmacology. *Biochemistry* 49, 10267–10276
- 390 Metz, J.T. and Hajduk, P.J. (2010) Rational approaches to targeted polypharmacology: creating and navigating protein–ligand interaction networks. *Curr. Opin. Chem. Biol.* 14, 498–504
- 391 Waring, M.J. (2010) Lipophilicity in drug discovery. *Expert Opin. Drug Discov.* 5, 235–248
- 392 Allen, J.A. and Roth, B.L. (2011) Strategies to discover unexpected targets for drugs active at G protein-coupled receptors. *Annu. Rev. Pharmacol. Toxicol.* 51, 117–144
- 393 von Eichborn, J. *et al.* (2011) PROMISCUOUS: a database for network-based drug-repositioning. *Nucleic Acids Res.* 39 (Database issue), D1060–D1066
- 394 Garcia-Serna, R. *et al.* (2011) iPHACE: integrative navigation in pharmacological space. *Bioinformatics* 26, 985–986
- 395 Leeson, P.D. and St-Gallay, S.A. (2011) The influence of the ‘organizational factor’ on compound quality in drug discovery. *Nat. Rev. Drug Discov.* 10, 749–765
- 396 Leeson, P.D. *et al.* (2011) Impact of ion class and time on oral drug molecular properties. *MedChemComm* 2, 91–105
- 397 Meanwell, N.A. (2011) Improving drug candidates by design: a focus on physicochemical properties as a means of improving compound disposition and safety. *Chem. Res. Toxicol.* 24, 1420–1456
- 398 Mestres, J. *et al.* (2011) Linking pharmacology to clinical reports: cyclobenzaprime and its possible association with serotonin syndrome. *Clin. Pharmacol. Ther.* 90, 662–665
- 399 Nisius, B. and Bajorath, J. (2011) Mapping of pharmacological space. *Expert Opin. Drug Discov.* 6, 1–7
- 400 Nonell-Canals, A. and Mestres, J. (2011) *In silico* target profiling of one billion molecules. *Mol. Inf.* 30, 405–409
- 401 Oprea, T.I. *et al.* (2011) Associating drugs, targets and clinical outcomes into an integrated network affords a new platform for computer-aided drug repurposing. *Mol. Inf.* 30, 100–111
- 402 Pérez-Nuño, V.I. and Ritchie, D.W. (2011) Using consensus-shape clustering to identify promiscuous ligands and protein targets and to choose the right query for shape-based virtual screening. *J. Chem. Inf. Model.* 51, 1233–1248
- 403 Prado-Prado, F. *et al.* (2011) 2D MI-DRAGON: a new predictor for protein–ligands interactions and theoretic-experimental studies of US FDA drug–target network, oxoisoporphine inhibitors for MAO-A and human parasite proteins. *Eur. J. Med. Chem.* 46, 5838–5851
- 404 Xie, L. *et al.* (2011) Structure-based systems biology for analysing off-target binding. *Curr. Opin. Struct. Biol.* 21, 189–199
- 405 Yang, L. *et al.* (2011) Chemical–protein interactome and its application in off-target identification. *Interdiscip. Sci.* 3, 22–30
- 406 Drewes, G. and Bantscheff, M., eds (2012) *Chemical Proteomics*, Springer
- 407 Hawley, S.A. *et al.* (2012) The ancient drug salicylate directly activates AMP-activated protein kinase. *Science* 336, 918–922
- 408 Lounkine, E. *et al.* (2012) Large-scale prediction and testing of drug activity on side-effect targets. *Nature* 486, 361–367
- 409 Pérez-Nuño, V.I. and Ritchie, D.W. (2012) Identifying and characterizing promiscuous targets: implications for virtual screening. *Expert Opin. Drug Discov.* 7, 1–17
- 410 Peters, J.U. *et al.* (2012) Can we discover pharmacological promiscuity early in the drug discovery process? *Drug Discov. Today* 17, 325–335
- 411 Simon, Z. *et al.* (2012) Drug effect prediction by polypharmacology-based interaction profiling. *J. Chem. Inf. Model.* 52, 134–145
- 412 Xie, L. *et al.* (2012) Novel computational approaches to polypharmacology as a means to define responses to individual drugs. *Annu. Rev. Pharmacol. Toxicol.* 52, 361–379
- 413 Wellendorph, P. *et al.* (2009) Molecular pharmacology of promiscuous seven transmembrane receptors sensing organic nutrients. *Mol. Pharmacol.* 76, 453–465
- 414 Li, X. *et al.* (2010) Extensive *in vivo* metabolite–protein interactions revealed by large-scale systematic analyses. *Cell* 143, 639–650
- 415 Li, X. and Snyder, M. (2011) Metabolites as global regulators: a new view of protein regulation: systematic investigation of metabolite–protein interactions may help bridge the gap between genome-wide association studies and small molecule screening studies. *Bioessays* 33, 485–489
- 416 Kell, D.B. (2011) Metabolites do social networking. *Nat. Chem. Biol.* 7, 7–8
- 417 Leeson, P.D. and Springthorpe, B. (2007) The influence of drug-like concepts on decision-making in medicinal chemistry. *Nat. Rev. Drug Discov.* 6, 881–890
- 418 Whitlock, G.A. *et al.* (2008) Pyridyl-phenyl ether monoamine reuptake inhibitors: impact of lipophilicity on dual SNRI pharmacology and off-target promiscuity. *Bioorg. Med. Chem. Lett.* 18, 2896–2899
- 419 Mestres, J. *et al.* (2009) The topology of drug–target interaction networks: implicit dependence on drug properties and target families. *Mol. Biosyst.* 5, 1051–1057
- 420 Price, D.A. *et al.* (2009) Physicochemical drug properties associated with *in vivo* toxicological outcomes: a review. *Expert Opin. Drug Metab. Toxicol.* 5, 921–931
- 421 Good, A.C. *et al.* (2012) Implications of promiscuous Pim-1 kinase fragment inhibitor hydrophobic interactions for fragment-based drug design. *J. Med. Chem.* 55, 2641–2648
- 422 Yang, Y. *et al.* (2010) Investigation of the relationship between topology and selectivity for druglike molecules. *J. Med. Chem.* 53, 7709–7714
- 423 Orengo, C.A. and Thornton, J.M. (2005) Protein families and their evolution – a structural perspective. *Annu. Rev. Biochem.* 74, 867–900
- 424 Mencher, S.K. and Wang, L.G. (2005) Promiscuous drugs compared to selective drugs (promiscuity can be a virtue). *BMC Clin. Pharmacol.* 5, 3
- 425 Gregori-Puigjané, E. and Mestres, J. (2008) A ligand-based approach to mining the chemogenomic space of drugs. *Comb. Chem. High Throughput Screen.* 11, 669–676
- 426 Hopkins, A.L. (2008) Network pharmacology: the next paradigm in drug discovery. *Nat. Chem. Biol.* 4, 682–690
- 427 Morphy, R. and Rankovic, Z. (2007) Fragments, network biology and designing multiple ligands. *Drug Discov. Today* 12, 156–160
- 428 Daws, L.C. (2009) Unfaithful neurotransmitter transporters: focus on serotonin uptake and implications for antidepressant efficacy. *Pharmacol. Ther.* 121, 89–99
- 429 Hu, Y. and Bajorath, J. (2010) Polypharmacology directed compound data mining: identification of promiscuous chemotypes with different activity profiles and comparison to approved drugs. *J. Chem. Inf. Model.* 50, 2112–2118
- 430 Seeman, P. (1972) The membrane actions of anesthetics and tranquilizers. *Pharmacol. Rev.* 24, 583–655
- 431 Franks, N.P. *et al.* (1998) Structural basis for the inhibition of firefly luciferase by a general anesthetic. *Biophys. J.* 75, 2205–2211
- 432 Patel, A.J. *et al.* (1999) Inhalational anesthetics activate two-pore-domain background K⁺ channels. *Nat. Neurosci.* 2, 422–426
- 433 Franks, N.P. and Lieb, W.R. (2004) Seeing the light: protein theories of general anesthesia. *Anesthesiology* 101, 235–237
- 434 Franks, N.P. and Honoré, E. (2004) The TREK K_{2P} channels and their role in general anaesthesia and neuroprotection. *Trends Pharmacol. Sci.* 25, 601–608
- 435 Heurteaux, C. *et al.* (2004) TREK-1, a K⁺ channel involved in neuroprotection and general anesthesia. *EMBO J.* 23, 2684–2695

REVIEWS

- 436 Grasshoff, C. *et al.* (2005) Molecular and systemic mechanisms of general anaesthesia: the 'multi-site and multiple mechanisms' concept. *Curr. Opin. Anaesthesiol.* 18, 386–391
- 437 Lobo, I.A. and Harris, R.A. (2005) Sites of alcohol and volatile anesthetic action on glycine receptors. *Int. Rev. Neurobiol.* 65, 53–87
- 438 Grasshoff, C. *et al.* (2006) Anaesthetic drugs: linking molecular actions to clinical effects. *Curr. Pharm. Des.* 12, 3665–3679
- 439 Franks, N.P. (2006) Molecular targets underlying general anaesthesia. *Br. J. Pharmacol.* 147 (Suppl. 1), S72–S81
- 440 Bertaccini, E.J. *et al.* (2007) The common chemical motifs within anesthetic binding sites. *Anesth. Analg.* 104, 318–324
- 441 Bonin, R.P. and Orser, B.A. (2008) GABA_A receptor subtypes underlying general anesthesia. *Pharmacol. Biochem. Behav.* 90, 105–112
- 442 Eckenhoff, R. *et al.* (2008) From anesthetic mechanisms research to drug discovery. *Clin. Pharmacol. Ther.* 84, 144–148
- 443 Franks, N.P. (2008) General anaesthesia: from molecular targets to neuronal pathways of sleep and arousal. *Nat. Rev. Neurosci.* 9, 370–386
- 444 Brannigan, G. *et al.* (2010) Multiple binding sites for the general anesthetic isoflurane identified in the nicotinic acetylcholine receptor transmembrane domain. *Proc. Natl. Acad. Sci. U.S.A.* 107, 14122–14127
- 445 Garcia, P.S. *et al.* (2010) General anesthetic actions on GABA(A) receptors. *Curr. Neuropharmacol.* 8, 2–9
- 446 Nury, H. *et al.* (2011) X-ray structures of general anaesthetics bound to a pentameric ligand-gated ion channel. *Nature* 469, 428–431
- 447 Werner, D.F. *et al.* (2011) Inhaled anesthetic responses of recombinant receptors and knockin mice harboring alpha2(S270H/L277A) GABA(A) receptor subunits that are resistant to isoflurane. *J. Pharmacol. Exp. Ther.* 336, 134–144
- 448 Shanmugasundararaj, S. *et al.* (2012) The location and nature of general anesthetic binding sites on the active conformation of firefly luciferase; a time resolved photolabeling study. *PLoS ONE* 7, E29854
- 449 Gasteiger, J., ed. (2003) *Handbook of Chemoinformatics: From Data to Knowledge*, Wiley/VCH
- 450 Bajorath, J., ed. (2004) *Chemoinformatics: Concepts, Methods and Tools for Drug Discovery*, Humana Press
- 451 Oprea, T.I., ed. (2004) *Chemoinformatics in Drug Discovery*, Wiley/VCH
- 452 Brown, N. *et al.* (2006) A chemoinformatics analysis of hit lists obtained from high-throughput affinity-selection screening. *J. Biomol. Screen.* 11, 123–130
- 453 Bender, A. *et al.* (2007) Analysis of pharmacology data and the prediction of adverse drug reactions and off-target effects from chemical structure. *ChemMedChem* 2, 861–873
- 454 Bunch, L. *et al.* (2009) Excitatory amino acid transporters as potential drug targets. *Expert Opin. Ther. Targets* 13, 719–731
- 455 Mok, N.Y. and Brenk, R. (2011) Mining the ChEMBL database: an efficient chemoinformatics workflow for assembling an ion channel-focused screening library. *J. Chem. Inf. Model.* 51, 2449–2454
- 456 Imming, P. *et al.* (2006) Drugs, their targets and the nature and number of drug targets. *Nat. Rev. Drug Discov.* 5, 821–834
- 457 Adams, R. *et al.* (2012) Binding sites in membrane proteins – diversity, druggability and prospects. *Eur. J. Cell Biol.* 91, 326–339
- 458 Mitcheson, J.S. *et al.* (2000) A structural basis for drug-induced long QT syndrome. *Proc. Natl. Acad. Sci. U.S.A.* 97, 12329–12333
- 459 Fermini, B. and Fossa, A.A. (2003) The impact of drug-induced QT interval prolongation on drug discovery and development. *Nat. Rev. Drug Discov.* 2, 439–447
- 460 Redfern, W.S. *et al.* (2003) Relationships between preclinical cardiac electrophysiology, clinical QT interval prolongation and torsade de pointes for a broad range of drugs: evidence for a provisional safety margin in drug development. *Cardiovasc. Res.* 58, 32–45
- 461 Deacon, M. *et al.* (2007) Early evaluation of compound QT prolongation effects: a predictive 384-well fluorescence polarization binding assay for measuring hERG blockade. *J. Pharmacol. Toxicol. Methods* 55, 238–247
- 462 Perrin, M.J. *et al.* (2008) Human ether-a-go-go related gene (hERG) K⁺ channels: function and dysfunction. *Prog. Biophys. Mol. Biol.* 98, 137–148
- 463 Raschi, E. *et al.* (2008) The hERG K⁺ channel: target and antitarget strategies in drug development. *Pharmacol. Res.* 57, 181–195
- 464 Ekins, S. *et al.* (2002) Three-dimensional quantitative structure-activity relationship for inhibition of human ether-a-go-go-related gene potassium channel. *J. Pharmacol. Exp. Ther.* 301, 427–434
- 465 Fernandez, D. *et al.* (2004) Physicochemical features of the hERG channel drug binding site. *J. Biol. Chem.* 279, 10120–10127
- 466 Sanguinetti, M.C. and Mitcheson, J.S. (2005) Predicting drug-hERG channel interactions that cause acquired long QT syndrome. *Trends Pharmacol. Sci.* 26, 119–124
- 467 Seierstad, M. and Agrafiotis, D.K. (2006) A QSAR model of hERG binding using a large, diverse, and internally consistent training set. *Chem. Biol. Drug Des.* 67, 284–296
- 468 Stansfeld, P.J. *et al.* (2006) Molecular mechanisms for drug interactions with hERG that cause long QT syndrome. *Expert Opin. Drug Metab. Toxicol.* 2, 81–94
- 469 Waring, M.J. and Johnstone, C. (2007) A quantitative assessment of hERG liability as a function of lipophilicity. *Bioorg. Med. Chem. Lett.* 17, 1759–1764
- 470 Priest, B.T. *et al.* (2008) Role of hERG potassium channel assays in drug development. *Channels (Austin)* 2, 87–93
- 471 Recanatini, M. *et al.* (2008) Modeling hERG and its interactions with drugs: recent advances in light of current potassium channel simulations. *ChemMedChem* 3, 523–535
- 472 Raschi, E. *et al.* (2009) hERG-related drug toxicity and models for predicting hERG liability and QT prolongation. *Expert Opin. Drug Metab. Toxicol.* 5, 1005–1021
- 473 Thai, K.M. and Ecker, G.F. (2009) Similarity-based SIBAR descriptors for classification of chemically diverse hERG blockers. *Mol. Divers.* 13, 321–336
- 474 Perry, M. *et al.* (2010) Revealing the structural basis of action of hERG potassium channel activators and blockers. *J. Physiol.* 588 (Pt 17), 3157–3167
- 475 Taboureau, O. and Jørgensen, F.S. (2011) In silico predictions of hERG channel blockers in drug discovery: from ligand-based and target-based approaches to systems chemical biology. *Comb. Chem. High Throughput Screen.* 14, 375–387
- 476 Zhou, P.Z. *et al.* (2011) Activation of human ether-a-go-go related gene (hERG) potassium channels by small molecules. *Acta Pharmacol. Sin.* 32, 781–788
- 477 Pirmohamed, M. *et al.* (2004) Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *BMJ* 329, 15–19
- 478 Davies, E.C. *et al.* (2009) Adverse drug reactions in hospital in-patients: a prospective analysis of 3695 patient-episodes. *PLoS ONE* 4, E4439
- 479 Wu, T.Y. *et al.* (2010) Ten-year trends in hospital admissions for adverse drug reactions in England 1999–2009. *J. R. Soc. Med.* 103, 239–250
- 480 Lazarou, J. *et al.* (1998) Incidence of adverse drug reactions in hospitalized patients – a meta-analysis of prospective studies. *JAMA* 279, 1200–1205
- 481 Juntti-Patinen, L. and Neuvonen, P.J. (2002) Drug-related deaths in a university central hospital. *Eur. J. Clin. Pharmacol.* 58, 479–482
- 482 Bender, A. *et al.* (2007) Chemogenomic data analysis: prediction of small-molecule targets and the advent of biological fingerprint. *Comb. Chem. High Throughput Screen.* 10, 719–731
- 483 Giacomini, K.M. *et al.* (2007) When good drugs go bad. *Nature* 446, 975–977
- 484 Berger, S.I. and Iyengar, R. (2009) Network analyses in systems pharmacology. *Bioinformatics* 25, 2466–2472
- 485 Scheiber, J. *et al.* (2009) Mapping adverse drug reactions in chemical space. *J. Med. Chem.* 52, 3103–3107
- 486 Scheiber, J. *et al.* (2009) Gaining insight into off-target mediated effects of drug candidates with a comprehensive systems chemical biology analysis. *J. Chem. Inf. Model.* 49, 308–317
- 487 Amur, S. *et al.* (2010) Pharmacogenomics and adverse drug reactions. *Personal. Med.* 7, 633–642
- 488 Berger, S.I. and Iyengar, R. (2010) Role of systems pharmacology in understanding drug adverse events. *Wiley Interdiscip. Rev. Syst. Biol. Med.* 3, 129–135
- 489 Niemi, M. (2010) Transporter pharmacogenetics and statin toxicity. *Clin. Pharmacol. Ther.* 87, 130–133
- 490 Wallach, I. *et al.* (2010) A structure-based approach for mapping adverse drug reactions to the perturbation of underlying biological pathways. *PLoS ONE* 5, E12063
- 491 Haller, C. and James, L.P. (2011) Adverse drug reactions: moving from chance to science. *Clin. Pharmacol. Ther.* 89, 761–764
- 492 Luo, H. *et al.* (2011) DRAR-CPI: a server for identifying drug repositioning potential and adverse drug reactions via the chemical-protein interactome. *Nucleic Acids Res.* 39, W492–W498
- 493 Pauwels, E. *et al.* (2011) Predicting drug side-effect profiles: a chemical fragment-based approach. *BMC Bioinf.* 12, 169
- 494 Tatonetti, N.P. *et al.* (2012) Data-driven prediction of drug effects and interactions. *Sci. Transl. Med.* 4, 125ra131
- 495 van der Greef, J. and McBurney, R.N. (2005) Rescuing drug discovery: *in vivo* systems pathology and systems pharmacology. *Nat. Rev. Drug Discov.* 4, 961–967
- 496 Oprea, T.I. *et al.* (2007) Systems chemical biology. *Nat. Chem. Biol.* 3, 447–450
- 497 Jamei, M. *et al.* (2009) The Simcyp population-based ADME simulator. *Expert Opin. Drug Metabol. Toxicol.* 5, 211–223
- 498 Janga, S.C. and Tzakos, A. (2009) Structure and organization of drug–target networks: insights from genomic approaches for drug discovery. *Mol. Biosyst.* 5, 1536–1548
- 499 Wist, A.D. *et al.* (2009) Systems pharmacology and genome medicine: a future perspective. *Genome Med.* 1, 11

- 500 Allerheiligen, S.R. (2010) Next-generation model-based drug discovery and development: quantitative and systems pharmacology. *Clin. Pharmacol. Ther.* 88, 135–137
- 501 Boran, A.D.W. and Iyengar, R. (2010) Systems approaches to polypharmacology and drug discovery. *Curr. Opin. Drug Discov. Dev.* 13, 297–309
- 502 Pujol, A. *et al.* (2010) Unveiling the role of network and systems biology in drug discovery. *Trends Pharmacol. Sci.* 31, 115–123
- 503 van der Graaf, P.H. and Benson, N. (2011) Systems pharmacology: bridging systems biology and pharmacokinetics–pharmacodynamics (PKPD) in drug discovery and development. *Pharm. Res.* 28, 1460–1464
- 504 Small, B.G. *et al.* (2011) Efficient discovery of anti-inflammatory small molecule combinations using evolutionary computing. *Nat. Chem. Biol.* 7, 902–908
- 505 Agoram, B.M. and Demin, O. (2012) Integration not isolation: arguing the case for quantitative and systems pharmacology in drug discovery and development. *Drug Discov. Today* 16, 1031–1036
- 506 Cucurull-Sanchez, L. *et al.* (2012) Relevance of systems pharmacology in drug discovery. *Drug Discov. Today* 17, 665–670
- 507 Dar, A.C. *et al.* (2012) Chemical genetic discovery of targets and anti-targets for cancer polypharmacology. *Nature* 486, 80–84
- 508 Haiech, J. *et al.* (2012) System biology and synthetic biology modify drug discovery and development. *Med. Sci. (Paris)* 28, 207–212
- 509 Hansen, J. *et al.* (2012) Systems pharmacology of complex diseases. *Ann. N. Y. Acad. Sci.* 1245, E1–E5
- 510 Mardinoglu, A. and Nielsen, J. (2012) Systems medicine and metabolic modelling. *J. Intern. Med.* 271, 142–154
- 511 O'Shea, P. (2012) Future medicine shaped by an interdisciplinary new biology. *Lancet* 379, 1544–1550
- 512 Panagiotou, G. and Taboureau, O. (2012) The impact of network biology in pharmacology and toxicology. *SAR QSAR Environ. Res.* 23, 221–235
- 513 Wild, D.J. *et al.* (2012) Systems chemical biology and the Semantic Web: what they mean for the future of drug discovery research. *Drug Discov. Today* 17, 469–474
- 514 Zhao, S. and Iyengar, R. (2012) Systems pharmacology: network analysis to identify multiscale mechanisms of drug action. *Annu. Rev. Pharmacol. Toxicol.* 52, 505–521
- 515 Kola, I. and Landis, J. (2004) Can the pharmaceutical industry reduce attrition rates? *Nat. Rev. Drug Discov.* 3, 711–715
- 516 Kola, I. (2008) The state of innovation in drug development. *Clin. Pharmacol. Ther.* 83, 227–230
- 517 Leeson, P.D. and Empfield, J.R. (2010) Reducing the risk of drug attrition associated with physicochemical properties. *Annu. Rep. Med. Chem.* 45, 393–407
- 518 Kwong, E. *et al.* (2011) Strategies for bringing drug delivery tools into discovery. *Int. J. Pharm.* 412, 1–7
- 519 Buzan, T. (2002) *How to Mind Map*. Thorsons
- 520 Liu, T. *et al.* (2007) BindingDB: a web-accessible database of experimentally determined protein–ligand binding affinities. *Nucleic Acids Res.* 35 (Database issue), D198–D201
- 521 de Matos, P. *et al.* (2010) Chemical entities of biological interest: an update. *Nucleic Acids Res.* 38 (Database issue), D249–D254
- 522 Gaulton, A. *et al.* (2012) ChEMBL: a large-scale bioactivity database for drug discovery. *Nucleic Acids Res.* 40 (Database issue), D1100–D1107
- 523 Taboureau, O. *et al.* (2010) ChemProt: a disease chemical biology database. *Nucleic Acids Res.* 39 (Database issue), D367–D372
- 524 Ji, Z.L. *et al.* (2003) Drug adverse reaction target database (DART): proteins related to adverse drug reactions. *Drug Saf.* 26, 685–690
- 525 Knox, C. *et al.* (2010) DrugBank 3.0: a comprehensive resource for 'omics' research on drugs. *Nucleic Acids Res.* 39, D1035–D1041
- 526 Roth, B.L. *et al.* (2004) Screening the receptorome to discover the molecular targets for plant-derived psychoactive compounds: a novel approach for CNS drug discovery. *Pharmacol. Ther.* 102, 99–110
- 527 Thorn, C.F. *et al.* (2010) Pharmacogenomics and bioinformatics: PharmGKB. *Pharmacogenomics* 11, 501–505
- 528 Gao, Z. *et al.* (2008) PDTD: a web-accessible protein database for drug target identification. *BMC Bioinformatics* 9, 104
- 529 Bashton, M. *et al.* (2008) PROCOGNATE: a cognate ligand domain mapping for enzymes. *Nucleic Acids Res.* 36 (Database issue), D618–D622
- 530 Li, Q. *et al.* (2010) PubChem as a public resource for drug discovery. *Drug Discov. Today* 15, 1052–1057
- 531 Canny, S.A. *et al.* (2012) PubChem promiscuity: a web resource for gathering compound promiscuity data from PubChem. *Bioinformatics* 28, 140–141
- 532 Yang, L. *et al.* (2009) SePreSA: a server for the prediction of populations susceptible to serious adverse drug reactions implementing the methodology of a chemical–protein interactome. *Nucleic Acids Res.* 37 (Web Server issue), W406–W412
- 533 Kuhn, M. *et al.* (2010) A side effect resource to capture phenotypic effects of drugs. *Mol. Syst. Biol.* 6, 343
- 534 Magariños, M.P. *et al.* (2012) TDR Targets: a chemogenomics resource for neglected diseases. *Nucleic Acids Res.* 40 (Database issue), D1118–D1127
- 535 Zhu, F. *et al.* (2012) Therapeutic target database update 2012: a resource for facilitating target-oriented drug discovery. *Nucleic Acids Res.* 40 (Database issue), D1128–D1136
- 536 Lim, E. *et al.* (2012) T3DB: a comprehensively annotated database of common toxins and their targets. *Nucleic Acids Res.* 38 (Database issue), D781–D786
- 537 Saier, M.H., Jr *et al.* (2009) The Transporter Classification Database: recent advances. *Nucleic Acids Res.* 37 (Database issue), D274–D278
- 538 Barbosa, A.J.M. and Del Rio, A. (2012) Freely accessible databases of commercial compounds for high-throughput virtual screenings. *Curr. Top. Med. Chem.* 12, 866–877
- 539 Xu, D. (2012) Protein databases on the internet. *Curr. Protoc. Mol. Biol.* Chapter 19, Unit 19.14
- 540 Hsiang, B. *et al.* (1999) A novel human hepatic organic anion transporting polypeptide (OATP2). Identification of a liver-specific human organic anion transporting polypeptide and identification of rat and human hydroxymethylglutaryl-CoA reductase inhibitor transporters. *J. Biol. Chem.* 274, 37161–37168
- 541 Ieiri, I. *et al.* (2009) Genetic polymorphisms of uptake (OATP1B1, 1B3) and efflux (MRP2, BCRP) transporters: implications for inter-individual differences in the pharmacokinetics and pharmacodynamics of statins and other clinically relevant drugs. *Expert Opin. Drug Metab. Toxicol.* 5, 703–729
- 542 Keskitalo, J.E. *et al.* (2009) ABCG2 polymorphism markedly affects the pharmacokinetics of atorvastatin and rosuvastatin. *Clin. Pharmacol. Ther.* 86, 197–203
- 543 Knauer, M.J. *et al.* (2010) Human skeletal muscle drug transporters determine local exposure and toxicity of statins. *Circ. Res.* 106, 297–306
- 544 Rodrigues, A.C. (2010) Efflux and uptake transporters as determinants of statin response. *Expert Opin. Drug Metab. Toxicol.* 6, 621–632
- 545 Siczekowski, E. *et al.* (2010) Double impact on P-glycoprotein by statins enhances doxorubicin cytotoxicity in human neuroblastoma cells. *Int. J. Cancer* 126, 2025–2035
- 546 Maggo, S.D. *et al.* (2011) Clinical implications of pharmacogenetic variation on the effects of statins. *Drug Saf.* 34, 1–19
- 547 Taubert, D. *et al.* (2006) Impact of P-glycoprotein on clopidogrel absorption. *Clin. Pharmacol. Ther.* 80, 486–501
- 548 Ellis, K.J. *et al.* (2009) Clopidogrel pharmacogenomics and risk of inadequate platelet inhibition: US FDA recommendations. *Pharmacogenomics* 10, 1799–1817
- 549 Momary, K.M. *et al.* (2010) Genetic causes of clopidogrel nonresponsiveness: which ones really count? *Pharmacotherapy* 30, 265–274
- 550 Floyd, C.N. *et al.* (2012) Comparative pharmacokinetics and pharmacodynamics of platelet adenosine diphosphate receptor antagonists and their clinical implications. *Clin. Pharmacokinet.* 51, 429–442
- 551 Lips, K.S. *et al.* (2005) Polyspecific cation transporters mediate luminal release of acetylcholine from bronchial epithelium. *Am. J. Respir. Cell Mol. Biol.* 33, 79–88
- 552 Chang, C. *et al.* (2006) Rapid identification of P-glycoprotein substrates and inhibitors. *Drug Metab. Dispos.* 34, 1976–1984
- 553 Horvath, G. *et al.* (2007) The effect of corticosteroids on the disposal of long-acting beta₂-agonists by airway smooth muscle cells. *J. Allergy Clin. Immunol.* 120, 1103–1109
- 554 Horvath, G. *et al.* (2011) Rapid nongenomic actions of inhaled corticosteroids on long-acting beta₂-agonist transport in the airway. *Pulm. Pharmacol. Ther.* 24, 654–659
- 555 Edwards, R.M. *et al.* (1999) Transport of [³H]losartan across isolated perfused rabbit proximal tubule. *J. Pharmacol. Exp. Ther.* 290, 38–42
- 556 Maeda, K. *et al.* (2006) Effects of organic anion transporting polypeptide 1B1 haplotype on pharmacokinetics of pravastatin, valsartan, and temocapril. *Clin. Pharmacol. Ther.* 79, 427–439
- 557 Yamashiro, W. *et al.* (2006) Involvement of transporters in the hepatic uptake and biliary excretion of valsartan, a selective antagonist of the angiotensin II AT₁-receptor, in humans. *Drug Metab. Dispos.* 34, 1247–1254
- 558 Yamashita, F. *et al.* (2006) Inhibitory effects of angiotensin II receptor antagonists and leukotriene receptor antagonists on the transport of human organic anion transporter 4. *J. Pharm. Pharmacol.* 58, 1499–1505
- 559 Knütter, I. *et al.* (2009) High-affinity interaction of sartans with H⁺/peptide transporters. *Drug Metab. Dispos.* 37, 143–149
- 560 Poirier, A. *et al.* (2009) Prediction of pharmacokinetic profile of valsartan in human based on *in vitro* uptake transport data. *J. Pharmacokinet. Pharmacodyn.* 36, 585–611

- 561 Simonson, S.G. *et al.* (2004) Rosuvastatin pharmacokinetics in heart transplant recipients administered an antirejection regimen including cyclosporine. *Clin. Pharmacol. Ther.* 76, 167–177
- 562 Ho, R.H. *et al.* (2006) Drug and bile acid transporters in rosuvastatin hepatic uptake: function, expression, and pharmacogenetics. *Gastroenterology* 130, 1793–1806
- 563 Windass, A.S. *et al.* (2007) The contribution of organic anion transporters OAT1 and OAT3 to the renal uptake of rosuvastatin. *J. Pharmacol. Exp. Ther.* 322, 1221–1227
- 564 Sharma, P. *et al.* (2012) Prediction of the *in vivo* OATP1B1-mediated drug–drug interaction potential of an investigational drug against a range of statins. *Eur. J. Pharm. Sci.* 47, 244–255
- 565 Boulton, D.W. *et al.* (2002) *In vitro* P-glycoprotein affinity for atypical and conventional antipsychotics. *Life Sci.* 71, 163–169
- 566 Wang, J.S. *et al.* (2004) Olanzapine penetration into brain is greater in transgenic Abcb1a P-glycoprotein-deficient mice than FVB1 (wild-type) animals. *Neuropsychopharmacology* 29, 551–557
- 567 Méary, A. *et al.* (2008) Pharmacogenetic study of atypical antipsychotic drug response: involvement of the norepinephrine transporter gene. *Am. J. Med. Genet. B: Neuropsychiatr. Genet.* 147B, 491–494
- 568 Lima, J.J. *et al.* (2006) Influence of leukotriene pathway polymorphisms on response to montelukast in asthma. *Am. J. Respir. Crit. Care Med.* 173, 379–385
- 569 Lima, J.J. (2007) Treatment heterogeneity in asthma: genetics of response to leukotriene modifiers. *Mol. Diagn. Ther.* 11, 97–104
- 570 Mougey, E.B. *et al.* (2009) Absorption of montelukast is transporter mediated: a common variant of OATP2B1 is associated with reduced plasma concentrations and poor response. *Pharmacogenet. Genom.* 19, 129–138
- 571 Roy, U. *et al.* (2009) Montelukast is a potent and durable inhibitor of multidrug resistance protein 2-mediated efflux of taxol and saquinavir. *Biol. Pharm. Bull.* 32, 2002–2009
- 572 Mougey, E.B. *et al.* (2011) Effect of citrus juice and SLCO2B1 genotype on the pharmacokinetics of montelukast. *J. Clin. Pharmacol.* 51, 751–760
- 573 Sachs, G. *et al.* (2006) Review article: the clinical pharmacology of proton pump inhibitors. *Aliment. Pharmacol. Ther.* 23 (Suppl. 2), 2–8
- 574 Saccar, C.L. (2009) The pharmacology of esomeprazole and its role in gastric acid related diseases. *Expert Opin. Drug Metab. Toxicol.* 5, 1113–1124
- 575 Thomas, J. *et al.* (2004) Active transport of imatinib into and out of cells: implications for drug resistance. *Blood* 104, 3739–3745
- 576 Burger, H. *et al.* (2005) Chronic imatinib mesylate exposure leads to reduced intracellular drug accumulation by induction of the ABCG2 (BCRP) and ABCB1 (MDR1) drug transport pumps. *Cancer Biol. Ther.* 4, 747–752
- 577 Ahlin, G. *et al.* (2008) Structural requirements for drug inhibition of the liver specific human organic cation transport protein 1. *J. Med. Chem.* 51, 5932–5942
- 578 Hu, S. *et al.* (2008) Interaction of imatinib with human organic ion carriers. *Clin. Cancer Res.* 14, 3141–3148
- 579 Chapuy, B. *et al.* (2009) ABC transporter A3 facilitates lysosomal sequestration of imatinib and modulates susceptibility of chronic myeloid leukemia cell lines to this drug. *Haematologica* 94, 1528–1536
- 580 Tanihara, Y. *et al.* (2009) Protective effect of concomitant administration of imatinib on cisplatin-induced nephrotoxicity focusing on renal organic cation transporter OCT2. *Biochem. Pharmacol.* 78, 1263–1271
- 581 Eechoute, K. *et al.* (2011) Drug transporters and imatinib treatment: implications for clinical practice. *Clin. Cancer Res.* 17, 406–415
- 582 Eechoute, K. *et al.* (2011) Environmental and genetic factors affecting transport of imatinib by OATP1A2. *Clin. Pharmacol. Ther.* 89, 816–820
- 583 Engler, J.R. *et al.* (2011) OCT-1 as a determinant of response to antileukemic treatment. *Clin. Pharmacol. Ther.* 89, 608–611
- 584 Gromicho, M. *et al.* (2011) Development of imatinib and dasatinib resistance: dynamics of expression of drug transporters ABCB1, ABCC1, ABCG2, MVP, and SLC22A1. *Leuk. Lymphoma* 52, 1980–1990
- 585 Wang, J.S. *et al.* (2006) Evaluation of antipsychotic drugs as inhibitors of multidrug resistance transporter P-glycoprotein. *Psychopharmacology (Berl.)* 187, 415–423
- 586 Nikisch, G. *et al.* (2011) Cytochrome P450 and ABCB1 genetics: association with quetiapine and norquetiapine plasma and cerebrospinal fluid concentrations and with clinical response in patients suffering from schizophrenia. A pilot study. *J. Psychopharmacol.* 25, 896–907