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 effecting 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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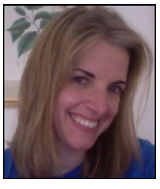
Douglas Kell took an MA (biochemistry) and DPhil (Oxon) in 1978. After several personal fellowships and other posts in what is now the University of Aberystwyth, he was awarded a Personal Chair (1992). He was a Founding Director of Aber Instruments Ltd (Queen's Award for Export Achievement, 1998). He 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 Bücher 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.

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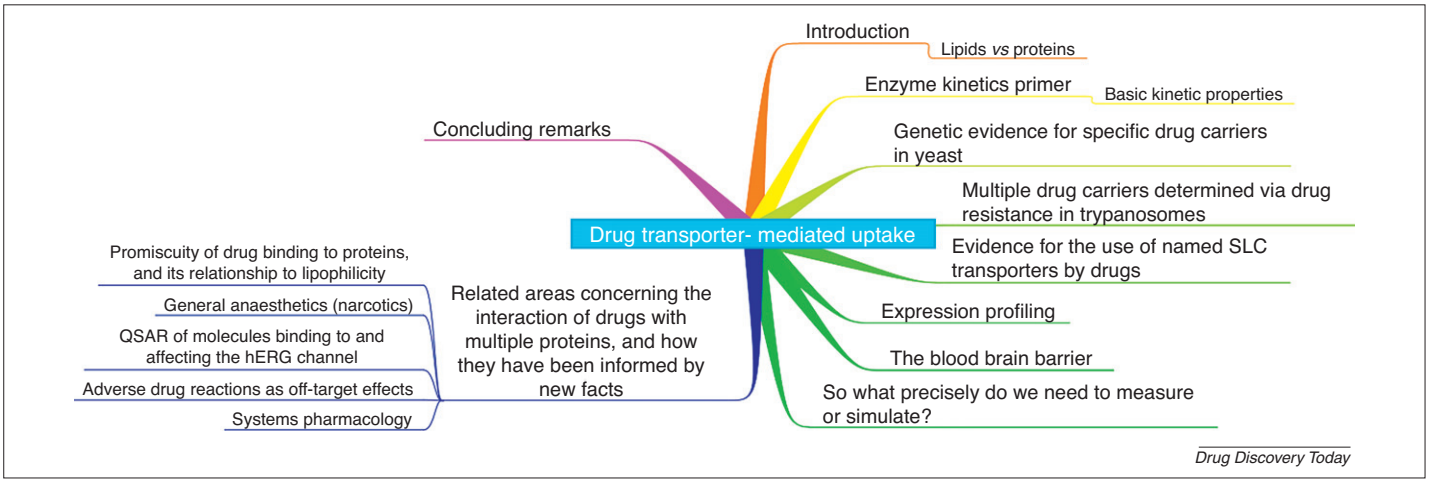


FIGURE 1

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 CO_2 [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 (solute carrier) 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: $K_{eq} = (V_{m,f} \cdot K_{m,r})/(V_{m,r} \cdot K_{m,f})$ [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 effecting 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 effected when the carrier was present. Figure 3 provides an example using diphenyleneiodonium, an NAD(P)H oxidase inhibitor [187,188] that seems to be taken up

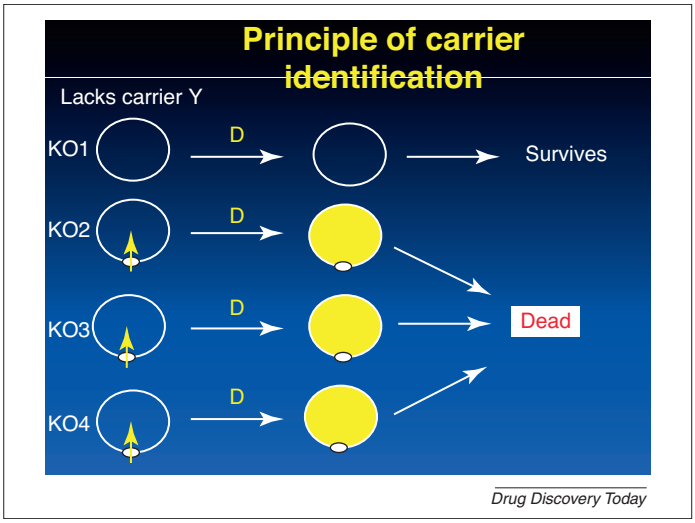


FIGURE 2

The principle of assessing carriers involved in drug uptake using the barcoded 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 Alsford *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 effected 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

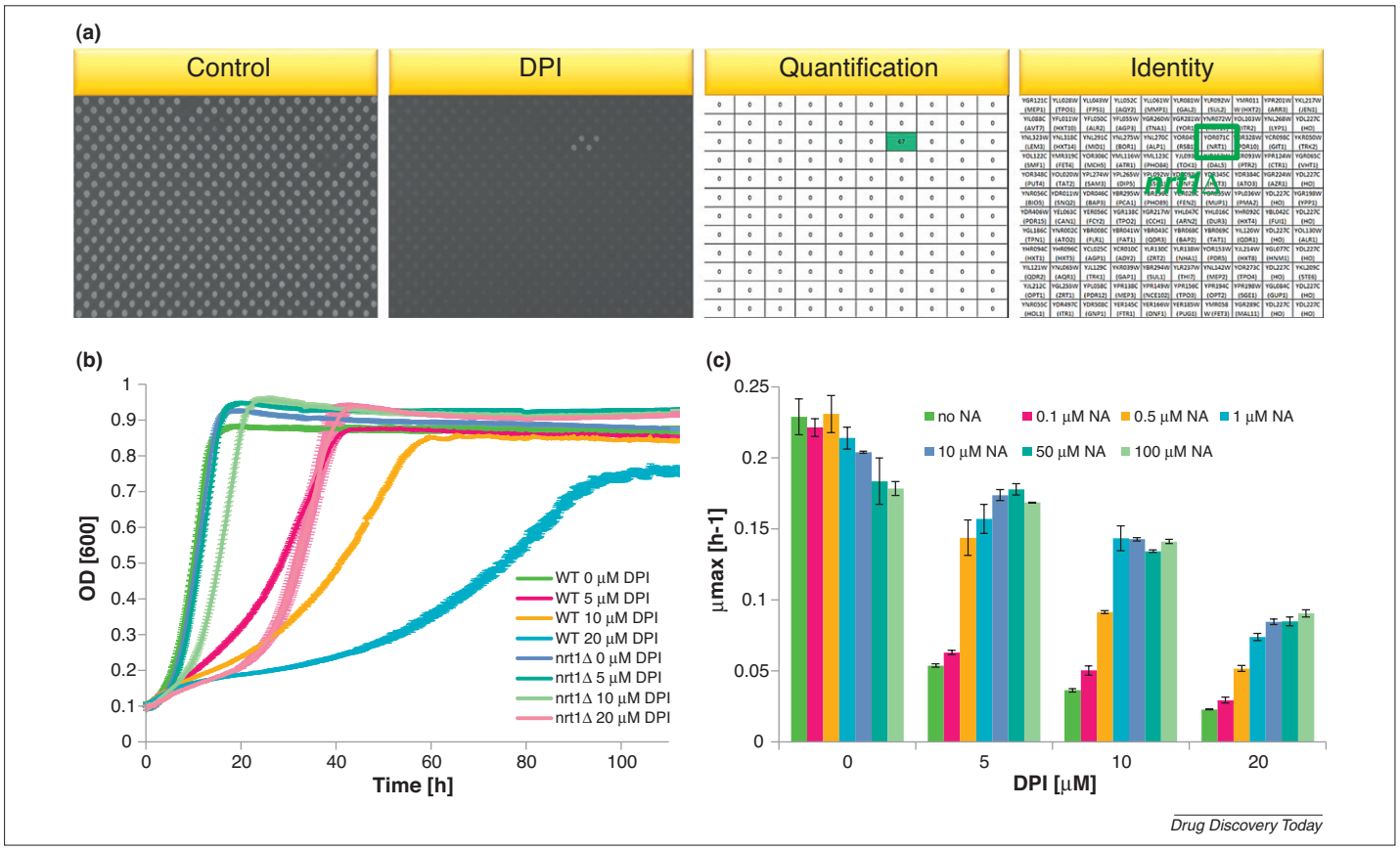


FIGURE 3

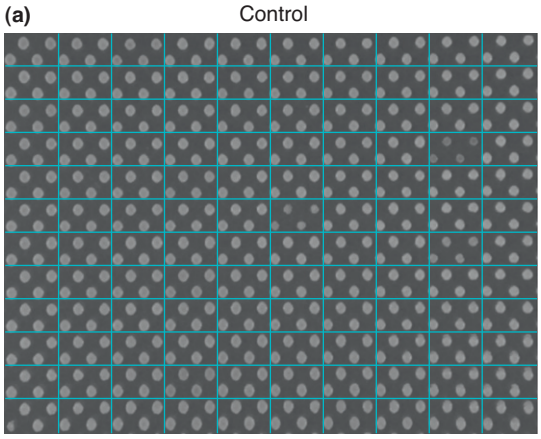
Identification and validation of the diphenyleneiodonium chloride (DPI) transporter, Nrt1p. **(a)** Array of diploid yeast (*Saccharomyces cerevisiae*) strains, each carrying a homozygous deletion for a gene encoding a plasmamembrane transporters. These were spotted (by a Singer RoToR© HAD robot) in quadruplicate onto synthetic medium plates containing 8 μM DPI or a solvent control. Strains lacking the gene encoding the nicotinamide riboside transporter Nrt1p (*nrt1*Δ) were able to grow in the presence of high-doses of DPI, suggesting that in the absence of Nrt1p, the drug can no longer enter yeast cells. **(b)** Growth curves of wild-type (WT) and *nrt1*Δ/*nrt1*Δ yeast strains in the presence of 0–20 μM DPI demonstrates that the absence of the proposed DPI transporter (Nrt1p) confers resistance to the drug. **(c)** Comparison of the maximum specific growth rate achieved by the WT strain in the presence of various concentrations of DPI and nicotinic acid (NA, a natural substrate of Nrt1p and consequently a competitor for this particular import route) confirms that in the presence of an alternative (or preferred) Nrt1p substrate, WT cells become resistant to higher doses of DPI, because the natural substrate outcompetes the drug for import by the transporter. Error bars = standard error of the mean; $n = 3$. See [181] for further experimental details.

that each is indeed known to interact with one or more transporter molecules.

In general, the correct approach to enzyme kinetics and systems biology is to see which transporters are expressed where, and to determine the structure–activity relationships for each of them (or at least those carrying the majority of the flux). Armed with this, one can create a suitable systems biology model [227–243] that accounts for the relevant fluxes (even in the absence of knowledge of detailed kinetics [244,245]). All else being equal, the flux via a specific carrier is determined by its intrinsic kinetic rate equation at the operating concentrations of the relevant substrates, products, and inhibitors multiplied by the concentration of the protein. We need to know something about all of these. Inferencing methods can allow one to estimate the important parameters [246–249] from measurements of fluxes and concentrations and a 'structural' (topological) model of the relevant networks [250–252].

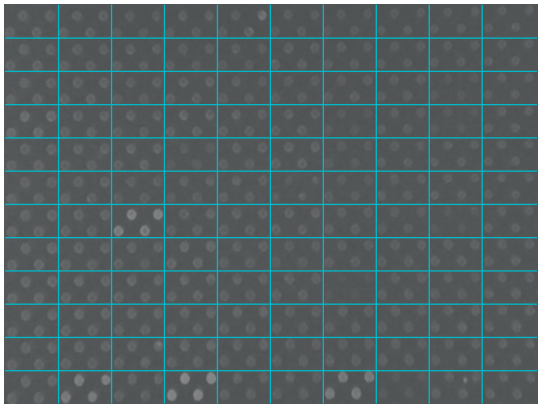
Expression profiling

It is now entirely straightforward to determine which gene products are expressed in which tissues, and this has been widely done at both transcriptomic and proteomic levels, including for transport proteins in tissues of interest to this community. As we mentioned before [5], it is known that the plasma membrane of Caco-2 cells contains several hundred transporters [253–258] of broad (and usually unknown) specificity, while the membranes of MDCK (Madin-Darby Canine Kidney) cells contain over 800 such proteins [259]. Expression profiling studies have also been carried out in different tissues, such as the BBB [260], in human intestine [261], in the proximal tubule [262], and in the NCI 60 cancer cell lines (where they can predict drug sensitivities [263], albeit that a more refined machine learning analysis [264] might have proved more effective). Other studies concentrate on transporter subsets [265,266], for example, of multidrug resistance (MDR) proteins [164] or the *SLCO* and *SLC22A* gene super-families [94], while further studies [267–269] are more global in nature and determine the expression of the cell surface proteome (of which transporters are a part). Together, such studies provide the data necessary to assess which transporters are expressed, differentially in which tissues. Similarly, antibody-based proteomics studies are providing considerable data on the tissue distributions of individual proteins [270,271], including for most of the known solute carrier families



(b) Identity

YGR121C (MEP1)	YLL028W (TPO1)	YLL043W (FPS1)	YLL052C (AQY2)	YLL061W (MMP1)	YLR081W (GAL2)	YLR092W (SUL2)	YMR011 W (HXT2)	YPR201W (ARR3)	YKL217W (JEN1)
YIL088C (AVT7)	YFL011W (HXT10)	YFL050C (ALR2)	YFL055W (AGP3)	YGR260W (TNA1)	YGR281W (YOR1)	YNR072W (HXT17)	YOL103W (ITR2)	YNL268W (LYP1)	YDL227C (HO)
YNL323W (LEM3)	YNL318C (HXT14)	YNL291C (MID1)	YNL275W (BOR1)	YNL270C (ALP1)	YOR049C (RSB1)	YOR071C (NRT1)	YOR328W (PDR10)	YCR098C (GIT1)	YKR050W (TRK2)
YOL122C (SMF1)	YMR319C (FET4)	YOR306C (MCH5)	YML116W (ATR1)	YML123C (PHO84)	YJL093C (TOK1)	YJR152W (DAL5)	YKR093W (PTR2)	YPR124W (CTR1)	YGR065C (VHT1)
YOR348C (PUT4)	YOL020W (TAT2)	YPL274W (SAM3)	YPL265W (DIP5)	YPL092W (SSU1)	YDR093W (DNF2)	YDR345C (HXT3)	YDR384C (ATO3)	YGR224W (AZR1)	YDL227C (HO)
YNR056C (BIO5)	YDR011W (SNQ2)	YDR046C (BAP3)	YBR295W (PCA1)	YBR296C (PHO89)	YCR028C (FEN2)	YGR055W (MUP1)	YPL036W (PMA2)	YDL227C (HO)	YGR198W (YPP1)
YDR406W (PDR15)	YEL063C (CAN1)	YER056C (FCY2)	YGR138C (TPO2)	YGR217W (CCH1)	YHL047C (ARN2)	YHL016C (DUR3)	YHR092C (HXT4)	YBL042C (FUI1)	YDL227C (HO)
YDL227C (HO)	YNR002C (ATO2)	YBR008C (FLR1)	YBR041W (FAT1)	YBR043C (QDR3)	YBR068C (BAP2)	YBR069C (TAT1)	YIL120W (QDR1)	YDL227C (HO)	YOL130W (ALR1)
YHR094C (HXT1)	YHR096C (HXT5)	YCL025C (AGP1)	YCR010C (ADY2)	YLR130C (ZRT2)	YLR138W (NHA1)	YOR153W (PDR5)	YJL214W (HXT8)	YGL077C (HNM1)	YDL227C (HO)
YIL121W (QDR2)	YNL065W (AQR1)	YJL129C (TRK1)	YKR039W (GAP1)	YBR294W (SUL1)	YLR237W (THI7)	YNL142W (MEP2)	YOR273C (TPO4)	YDL227C (HO)	YKL209C (STE6)
YJL212C (OPT1)	YGL255W (ZRT1)	YPL058C (PDR12)	YPR138C (MEP3)	YPR149W (NCE102)	YPR156C (TPO3)	YPR194C (OPT2)	YPR198W (SGE1)	YGL084C (GUP1)	YDL227C (HO)
YNR055C (HOL1)	YDR497C (ITR1)	YDR508C (GNP1)	YER145C (FTR1)	YER166W (DNF1)	YER185W (PUG1)	YMR058 W (FET3)	YGR289C (MAL11)	YDL227C (HO)	YDL227C (HO)



(d) Quantification

1	2	0	1	15	0	0	0	0	0
1	0	3	0	1	3	0	0	0	0
2	3	0	2	0	0	1	0	0	0
32	3	0	3	1	1	0	0	0	0
4	2	7	0	0	4	0	0	2	0
1	4	0	0	0	2	0	0	1	0
7	2	73	4	1	4	0	0	0	0
7	2	2	15	1	0	0	0	1	0
6	2	3	3	0	3	0	0	0	1
3	2	1	1	2	0	0	0	0	1
4	2	7	6	1	0	1	0	1	0
0	81	0	85	0	1	77	0	13	0

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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	3.673	[520]
ChEBI	http://www.ebi.ac.uk/chebi/init.do	>28,000		[521]
ChEMBL	https://www.ebi.ac.uk/chembldb/	>1 million	>8.800	[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/	6.711	4.227	[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	>1.600 assays	[530]
PubChem promiscuity	http://chemutils.florida.scripps.edu/pcpromiscuity			[531]
SePreSA	http://sepresa.bio-x.cn/			[532]
SIDER2	http://sideeffects.embl.de/	996	4.199	[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/ttd/	17,816	2.015	[535]
Toxin, toxin-target database (T3DB)	http://www.t3db.org/	2900	1.300	[536]
Transporter Classification DataBase (TCDB)	http://tcdb.org/			[537]

Some others are listed, for example in [457,538,539,587]. 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

TABLE 2

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

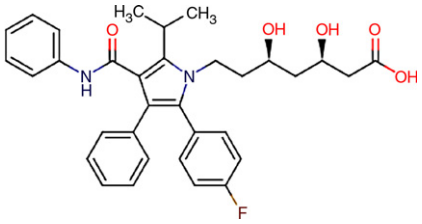
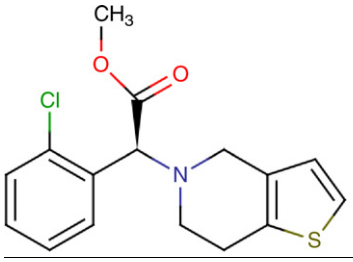
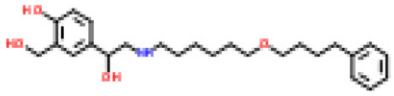
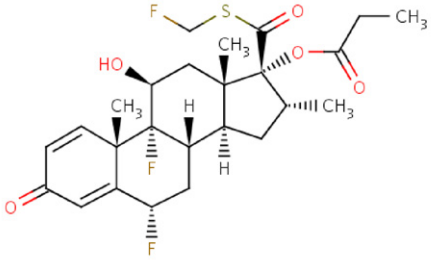
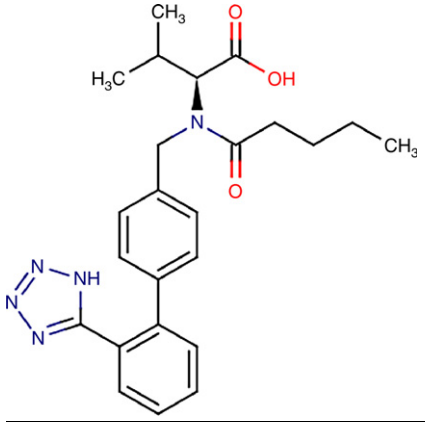
Drug name	Disease area	Annual Sales (2010) in $Bn	Known transporter (family) interaction(s)	Representative references
Lipitor (atorvastatin) 	Cardiovascular	10.7	ABCB1 ABCC1 ABCC4 ABCC5 ABCG2 SLCO1A2 SLCO1B1	[94,489,540–546]
Plavix (clopidogrel) 	Cardiovascular	9.5	ABCB1	[547–550]
Seretide/Advair (salmeterol 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*)

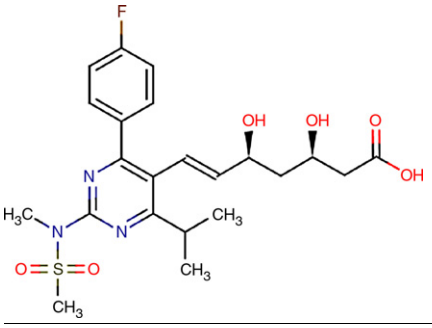
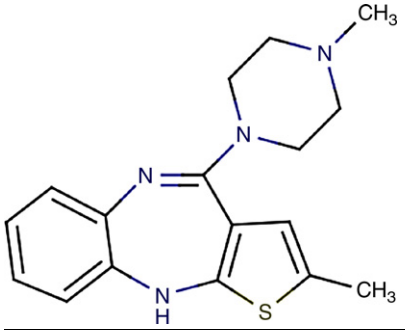
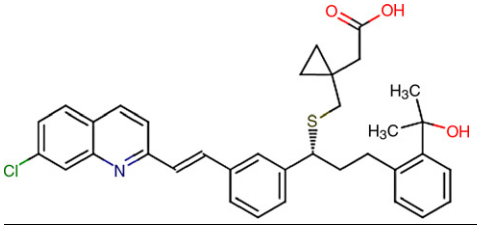
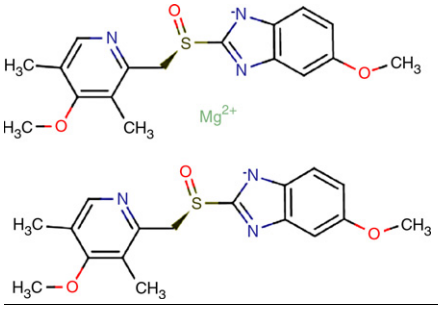
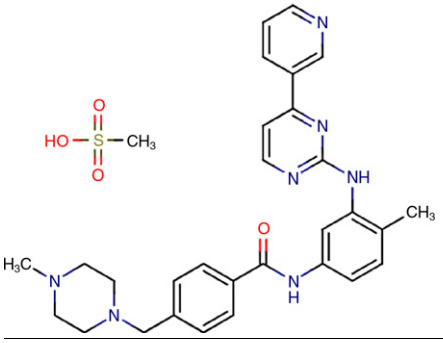
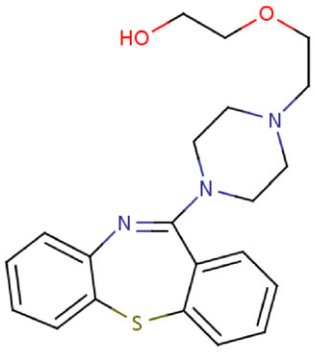
Drug name	Disease area	Annual Sales (2010) in $Bn	Known transporter (family) interaction(s)	Representative references
Crestor (rosuvastatin) 	Cardiovascular	5.7	ABCC1 ABCC4 ABCG2 SLCO1A2 SLCO1B1 SLCO1B3	[27,94,489,541–544, 546,561–564]
Zyprexa (olanzapine) 	CNS	5.1	ABCB1 SLC6A2	[565–567]
Singulair (montelukast) 	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/chembldb/), 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 that were 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 lipophilicity 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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