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The transporter-mediated cellular uptake of pharmaceutical drugs is based on their metabolite-likeness and not on their bulk biophysical properties: Towards a systems pharmacology☆

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Summary Several recent developments are brought together: (i) the new availability of a consensus, curated human metabolic network reconstruction (Recon2), approximately a third of whose steps are represented by transporters, (ii) the recognition that most successful (marketed) drugs, as well as natural products, bear significant similarities to the metabolites in Recon2, (iii) the recognition that to get into and out of cells such drugs hitchhike on the transporters that are part of normal intermediary metabolism, and the consequent recognition that for intact biomembrane Phospholipid Bilayer diffusion Is Negligible (PBIN), and (iv) the consequent recognition that we need to exploit this and to use more phenotypic assays to understand how drugs affect cells and organisms. I show in particular that lipophilicity is a very poor predictor of drug permeability, and that we need to (and can) bring together our knowledge of both pharmacology and systems biology modelling into a new systems pharmacology.

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Introduction

A current development, stemming from the widely recognised decreases in productivity of the pharmaceutical industry (e.g., Kola and Landis, 2004; van der Greef and McBurney, 2005; Kola, 2008; Empfield and Leeson, 2010; Kell, 2013; Cook et al., 2014; Hay et al., 2014), recognises that we need to understand the interactions of drugs and organisms not via a reductionist, hypothesis-dependent approach (Kell and Oliver, 2004) but (not least because of the complexity of such systems, Kell, 2012; Kell and Lurie Luke, 2015) from a systems biology point of view.

As well as a recognition of the need for hitting multiple targets simultaneously, whether via cocktails of drugs or via polypharmacology (Achenbach et al., 2011; Bottegoni et al., 2012; Mestres and Gregori-Puigjané, 2009; Metz and Hajduk, 2010; Milletti and Vulpetti, 2010; Plake and Schroeder, 2011; Simon et al., 2012; Xie et al., 2012; Hopkins, 2008, 2009), we thus also need to move more towards phenotypic screening (Kell, 2013; García-Bustos and Gamo, 2011; Jenkins and Urban, 2010; Klekota et al., 2005; Laggner et al., 2012; Stine et al., 2011; Swinney, 2013a; Zhang et al., 2014) (as was classically the case in pharmacology, Keiser et al., 2010 and is in fact still so today, Swinney, 2013a,b; Swinney and Anthony, 2011).

Although most laboratories were brought up with — and sported on their walls — the printed biochemical wallcharts that summarised the metabolic pathways then known (Michal, 1999), it is only more recently that digitally available metabolic databases (Ooi et al., 2010) have come to the fore (e.g., ChEBI, Degtyarenko et al., 2009; de Matos et al., 2012; Hastings et al., 2013, HMDB, Wishart et al., 2013, KEGG, Kanehisa et al., 2012, 2014, MetaCyc, Karp et al., 2013; Altman et al., 2013; Caspi et al., 2014 and MetabolLights, Haug et al., 2013). In particular, the recent availability of a highly curated consensus map of the human metabolic network (and thus intermediary metabolites) (Thiele et al., 2013; Swainston et al., 2013; Kell and Goodacre, 2014), based on a similar exercise in baker's yeast (Herrgård et al., 2008), has become available. Fully one third of the enzymatic steps these contain involve transport reactions.

Armed with such data, another recent development is the recognition that most marketed drugs bear structural similarities to known human metabolites, and more so than do the typical structures found in drug discovery libraries (e.g., Feher and Schmidt, 2003; Karakoc et al., 2006; Gupta and Aires-de-Sousa, 2007; Dobson et al., 2009a,b; Khanna and Ranganathan, 2009, 2011; Peironcely et al., 2011; Zhang et al., 2011; Chen et al., 2012; Walters, 2012; Hamdalla et al., 2013; O'Hagan et al., 2015a,b). Arguably consistent with this, one might also comment on the fact that natural products remain a major source of successful (marketed) pharmaceutical drugs (Baker et al., 2007; Bohlin et al., 2010; Butler, 2008; Carlson, 2010; Cragg et al., 1997; Ertl and Schuffenhauer, 2008; Ganesan, 2008; Harvey, 2008; Huang et al., 2013; Kingston, 2011; Koch et al., 2005; Koehn and Carter, 2005; Lam, 2007; Li and Vederas, 2009; Newman et al., 2003; Newman and Cragg, 2007, 2012; Paterson and Anderson, 2005; Rosén et al., 2009; Singh et al., 2009; Wetzel et al., 2007; Newman, 2011; Camp et al., 2012; Cordell and Colvard, 2012; Dias et al., 2012; Jayaseelan et al., 2012; Zhu et al., 2012; Cragg and Newman, 2013; Gu et al., 2013; Over et al., 2013; Du et al., 2014; Pascolutti and Quinn, 2014).

Finally, and bringing the above together, there is an emerging recognition that drugs normally get into (and out of) cells by hitch-hiking on the transporters that are there not (in evolutionary terms) for the benefit of pharmaceutical companies but for the purposes of intermediary metabolism (see e.g., Kell, 2013; Kell and Goodacre, 2014; Dobson et al., 2009a,b; Dobson and Kell, 2008; Dobson et al., 2009a,b; Kell and Dobson, 2009; Giacomini et al., 2010; Giacomini and Huang, 2013; Kell et al., 2011, 2013; Lanthaler et al., 2011; Giacomini and Huang, 2013; Kell and Oliver, 2014; Kell, 2015). The same is true for the huge number of molecules of biotechnological interest (Kell, 2015; Kell et al., 2015), and even for small molecules such as CO_2 (Kaldenhoff et al., 2014; Kai and Kaldenhoff, 2014).

Despite this, there is a widespread belief that drugs mainly get into cells on the basis of their lipophilicity (Seeman, 1972), by crossing whatever phospholipid bilayer portions of membranes may be present. Although (as far as I am aware) Chris Lipinski never wrote any such thing, the basis of the famous 'rule of 5' (Lipinski et al., 1997) is taken to assume this, albeit Lipinski did state (Owens and Lipinski, 2003) that if transporters (or natural products) were involved then rule(s) did not apply. At all events, it is widely believed that because of this 'phospholipid diffusion' model for the 'background' rates of drug transport, there are good correlations between a drug's lipophilicity and the