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editorial

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Druggability: selecting optimized drug candidates

In the drug discovery arena, the term 'druggability' has been used in the following ways:

(i) To refer to the druggable genome and druggable proteins (molecular targets). Now that we know the size of the human genome, it is important to estimate how many drug-targeted proteins there might be. In this issue of *Drug Discovery Today*, Russ and Lampel give an overview of the druggable genome and its implications for some well-established approaches in drug discovery. They make no claims of biological completeness and do not preach the superiority of gene-driven over function-driven drug discovery. Hajduk and colleagues describe how to identify highly druggable proteins and use this information in target identification and validation campaigns. They also discuss strategies for the optimal integration of protein druggabilility data with bioinformatic approaches to target selection.

(ii) To indicate the druggability of compounds. Drug candidates have a high rate of attrition during discovery and development because of their lack of 'drug-like properties'. Drug-like properties are the physicochemical (e.g. solubility, stability) and biological [i.e. absorption, distribution, metabolism, elimination and toxicity (ADME–Tox)] characteristics that are consistent with good clinical performance [1,2]. Therefore, pharmaceutical companies try to avoid any potential problems and have been implementing profiling programs to examine pharmaceutical properties earlier in the drug discovery process. The physicochemical properties that are necessary to increase the likelihood of oral bioavailability have been formalized into the 'rule of five' by Lipinski *et al.* [3].

The characteristics of druggable compounds should be such that they can be delivered effectively to the target tissues and cells. In this issue, Petrak shows that successful development of site-selective drug delivery systems will need to include the development of not only suitable carriers, but also drug entities that meet the pharmacokinetic demands for this application. Practical drug-carrier systems need to be free of nonspecific interactions, have access to and accumulate at the target site, and deliver an active drug that would actually benefit from targeting.

Here, I will give a short description of 'druggability of compounds' in terms of selecting optimized drug candidates.

Drug metabolism and pharmacokinetic properties

The pharmacokinetic (ADME) profile should be a primary consideration in the selection of a drug candidate, ultimately contributing to its eventual clinical

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success or failure. It is now recognized that selection of a 'robust' candidate requires a balance between efficacy, safety and drug metabolism and pharmacokinetic (DMPK) properties, and that the screening of these characteristics should be carried out as early as possible in the discovery process. Thus, many pharmaceutical companies are now systematically carrying out rational high-throughput DMPK screening and establishing pharmacokinetic selection criteria. For example, HTS for intestinal absorption using Caco-2 cells and screening for metabolic stability and metabolic enzyme inhibition using cytochrome P450 recombinant microsomes or human liver microsomes have become extremely popular. Attention is now being focused on optimizing the pharmacokinetic profiles of drug candidates using transporter function [4–7].

In 2003, Frank and Hargreaves [8] summarized the reasons for attrition during clinical development and found that the percentage of projects involving new chemical entities (NCEs) failing because of pharmacokinetic and bioavailability (e.g. DMPK) reasons dropped from 40% in 1991 to 10% in 2000. By contrast, those failing because of the efficacy, toxicology and clinical safety remain almost the same, that is, 30%, 20% and 10%, respectively. This decrease in attrition rate because of DMPK reasons is considered reasonable, taking into account that in many pharmaceutical industries, as described above, screening for DMPK properties, including absorption, metabolic stability and drug–drug interactions, began more than 15 years ago. Considering that the transporter properties have not been incorporated yet into the current DMPK screening process, except for the screening of substrates and inhibitors for P-glycoprotein, the screening of NCEs in terms of the transporter properties in the liver, kidney, intestine and in the target tissues might be able to reduce further the attrition rate for DMPK reasons.

Drug transporters

It has been shown that some drug transporters are responsible for drug transport in various tissues such as the intestine, liver, kidney and target tissues (e.g. brain, tumors) and they might be key determinants of the pharmacokinetic characteristics of a drug as far as its intestinal absorption, tissue distribution, and elimination are concerned. The tissue distribution and elimination route of some drugs is determined by the degree of expression of each transporter subtype in each tissue and its corresponding substrate affinity and transporting capacity. Thus, regulating the function of transporters should allow efficient development of drugs that have ideal pharmacokinetic profiles. As drug discovery involving the use of transport mechanisms increases, the need for an effective *in vitro* screening system for transporters will also increase. Accordingly, methods allowing the rational prediction and extrapolation of *in vivo* drug disposition from *in vitro* data are urgently required. For successful drug discovery, development and targeting we have to know which transporters play a role in the disposition of a drug and its subsequent effects. In that sense, the use of newly established 'doubly transfected' cells [9–11], which express the uptake transporter and efflux transporter on the basal and apical membrane of the cells, respectively, and mimic the vectorial transport of NCEs in epithelia cells (liver, kidney and intestine), should be considered for use as an appropriate screening tool.

Conclusions

Contrary to some opinions, complete reliance on *in vitro* or *in silico* screens can actually slow down a discovery program, mainly because DMPK is an emerging science and much about the biochemistry and cell biology relating to DMPK is still poorly understood. Thus, it is important to have *in vivo* reality checks as often as possible, at all stages of the discovery process [12].

Finally, I want to make a proposal regarding the importance of integrating ADME screening information and the screening information about pharmacological and toxicological activities. Such an approach, which could be called 'quantitative integrated drug selection method' (QIDSM) needs to be developed. For example, you might not be able to expect a compound to be ranked highest for all the properties, including dissolution, absorption, metabolism, excretion, drug–drug interaction, interindividual variability, high permeability in the pharmacological target tissue and low permeability in the toxicological target tissue, high intrinsic pharmacological activity and least toxicological activity. In the current drug discovery process, you have all these screening data obtained *in vitro* and *in vivo* (preclinical). Nevertheless, no rational method to scientifically select compounds which should go on to clinical Phase I studies has been established yet. To make this process scientific, mechanism-based pharmacokinetic and pharmacodynamic modeling [13,14], incorporating all of these screened parameters, should be established.

In future, instead of *in vitro* measurements you might be able to use *in silico* methods to obtain some parameters, if you find the method reliable. Furthermore, by using *in silico* screening methods, compounds with poor ADME properties should be excluded from chemical libraries and the so-called 'value-added library' should be increased. From such libraries, NCEs with very good ADME properties should be selected with the use of reliable screening methods.

Also, although extensive and comprehensive screening procedures might place a heavy burden not only on DMPK scientists but also on discovery chemists, pharmacologists and toxicologists, it greatly increases the chance that NCEs will eventually become marketed drugs.

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