OPINION

# Drug research: myths, hype and reality

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Lack of success with early combinatorial chemistry and high-throughput screening approaches resulted from inappropriate compound selection. We are now aware that screening compounds should be either 'lead-like' or 'drug-like' and have the potential to be orally available. However, there is a growing tendency to misuse such terms and to overestimate their importance, and to overemphasize ADME problems in clinical failure. Sometimes, this goes hand-in-hand with an uncritical application of high-throughput *in silico* methods. Structure-based and computer-aided approaches can only be as good as the medicinal chemistry they are based on. The search for new drugs, especially in lead optimization, is an evolutionary process that is only likely to be successful if new methods merge with classical medicinal chemistry knowledge.

In a recent perspective[1], David Horrobin raised the question of whether drug researchers are already living in Hermann Hesse's virtual land Castalia, where the masters organise and play a game that is highly sophisticated and brilliant, but which makes no contribution to real world issues. His criticism refers to a lack of congruence between *in vitro* and animal models and the corresponding human diseases. However, this seems to be only one of several areas of current drug research in which the 'games' drift away from reality, and only one reason for failure in drug discovery[2]. Whenever a new concept or technology emerges, people get excited, jump on it and expect that new drugs will result more or less automatically, without having validated the new game. The new paradigm is considered to be more promising for delivering novel drugs than focusing on core expertise in drug discovery. In addition, as discussed here, the drug discovery scene is covered with a mist of myths, hype and false conclusions.

## Is there a 'druggable genome'?

The main difference between drug research in the past two or three decades, and that before this period, is the focus on molecular targets. When the human genome project was initiated, the pharmaceutical industry eagerly awaited its results, expecting a myriad of promising new targets. Bioinformatics, applied to the human genome sequence, was anticipated to provide a platform to fight all kinds of diseases. Consulting companies and start-ups predicted that a tidal wave of novel targets would sweep over the pharmaceutical industry, leaving unprecedented numbers of innovative drugs in its wake. However, the outcome so far has not lived up to these expectations[2].

On the other hand, many were disappointed when it became clear that our genome contains only ~30,000 genes, instead of the expected 100,000. But does this really matter? The answer is no. Nearly all drugs act at the protein level, at least in their first step. Fortunately, the proteome is much larger than the genome, due to alternative splicing and post-translational modifications. Furthermore, drug targets are often protein complexes, made up from a few protein chains (for example, the integrins, nicotinic ACh-regulated ion channels, heterodimeric receptors and so on). As a consequence, there are several hundred thousand potential targets. If we add signalling pathways, many more possibilities for drug intervention result. The term 'druggable genome'[3] is therefore misleading. We should look at the druggable proteome or, more precisely, the druggable 'targetome'. We need not fear having too few targets in the future, even if only a small percentage of these targets are indeed druggable.

## Is a target focus always best?

With the advent of *in vitro* test systems about 30 years ago, and the development of high-throughput screening (HTS) and ultra-HTS models, drug research shifted from animal studies to target-oriented research. This strategy works well in cases in which a certain disease is related to a unique target that can be modulated by a small molecule. A recent example is the BCR–ABL kinase inhibitor imatinib (Gleevec; Novartis), which inhibits a constitutively active kinase that is present only in patients with chronic myelogenous leukaemia. But most of our drugs act in a quite indirect manner or at a distant site. The popular statins, prescribed to decrease pathologically elevated cholesterol levels, interfere with cholesterol biosynthesis at the $C_5$ level (hydroxymethyl glutarate), and therefore interfere with the biosynthesis of farnesyl residues, cholic acids, sexual hormones and corticosteroids; it is really surprising that these drugs do not produce more severe side effects. Olanzapine, a successful neuroleptic and one of the 20 top-selling drugs, acts as a highly unspecific, nanomolar antagonist of at least ten different neurotransmitter receptors. Some time ago, such active agents were belittled as 'dirty drugs', whereas we now understand that in certain cases a balanced activity at several targets might be better suited for therapy than high specificity. The first beta-blockers were unspecific $\beta_1$ and $\beta_2$ antagonists; later, $\beta_1$-specific antagonists, as well as partial agonists, with and without $\alpha_1$-antagonistic activity, resulted from these early leads and were introduced into therapy. So, if we look at the number of potential targets, we could even consider certain receptor combinations as 'targets' — the druggable

'physiome', yet another 'ome' in the ever-burgeoning '-omics' lexicon. However, this would demand a shift in the mind-set of drug researchers: the abandonment of the classical 'one compound–one target' relationship.

### Is poor ADME the main problem?

Combinatorial chemistry was expected to generate new drugs just by virtue of the sheer size of the libraries produced. In fact, the opposite turned out to be the case[4]: in the early days, many large and greasy, biologically inactive molecules were produced and tested, most often as ill-defined mixtures. Library composition has subsequently been significantly influenced by Chris Lipinski, who formulated simple rules for predicting which compounds would have a high risk of poor bioavailability[5]. According to Lipinksi's 'rule of five', drug candidates should have a molecular mass below 500 Daltons, a lipophilicity below log P = 5, and contain no more than 5 hydrogen bond donors and no more than 10 oxygen and nitrogen atoms; poor passive absorption is to be expected if two or more of these conditions are violated. As an alternative to the Lipinski rules, polar surface area[6] or VolSurf parameters[7] can be used to predict oral absorption[6–9] and blood–brain barrier penetration[7,8]. The flexibility of molecules has been recognized as another factor influencing bioavailability[10]. A recent comparison of drugs under clinical development shows a steady decrease of molecular mass, number of hydrogen bond acceptors and, to some extent, the number of rotatable bonds, in moving from Phase I clinical studies to later phases and, finally, to marketed drugs[11]. Whereas this could indicate a higher attrition rate of large, flexible compounds rich in hydrogen-bond acceptors, it might also result from an increase in the number of development candidates having such properties in the past few years.

Violation of the Lipinski rules was indeed the main reason for failure of early combinatorial libraries, and the application of the rules significantly aided improvements in their quality. In this context, two investigations are most often cited[12,13], which correlated about 40% of failures in clinical development with inappropriate pharmacokinetics, that is, a lack of sufficient oral efficacy. Correspondingly, absorption, distribution, metabolism and excretion (ADME) parameters are now considered to be key factors in drug development (FIG. 1a). However, is this presumption really true? A closer inspection of the data reveals that a high fraction of failures attributed to poor ADME characteristics resulted from a relatively large number of poorly bioavailable anti-infectives[13]. If these compounds are removed, inappropriate ADME properties were responsible only for a 7% attrition rate (FIG. 1b). Although it has to be admitted that, in principle, it might be problematic to differentiate between a 'lack of clinical efficacy' resulting from a lack of activity, insufficient pharmacokinetics and/or unfavourable organ or tissue distribution, inappropriate ADME characteristics have clearly made far less of a contribution to clinical failures than is widely supposed! Moreover, today, with increasing awareness of appropriate compound properties, with high-throughput *in vitro* test systems for solubility and permeability, and the decreasing interest in peptide-like drug structures, this proportion is likely to be even smaller. However, the old figures including the anti-infectives are still very frequently cited (for example, REF. 14), because these are better suited to backing up the hype related to *in silico* drug discovery.

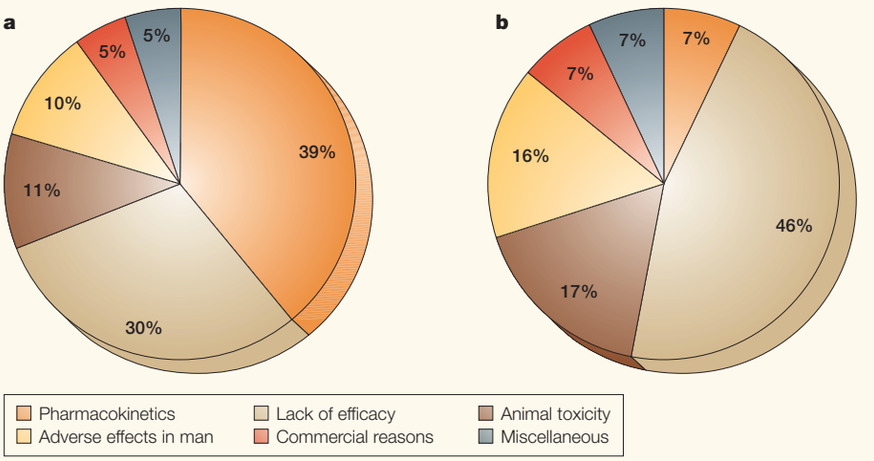



Figure 1 | **Reasons for failure in drug development. a** | 198 NCEs in clinical development by large UK companies, 1964–1985. **b** | 121 NCEs, excluding the anti-infectives from diagram **a**. (Source: Centre for Medicines Research; redrawn from REF. 13).

### Are we using the right VS techniques?

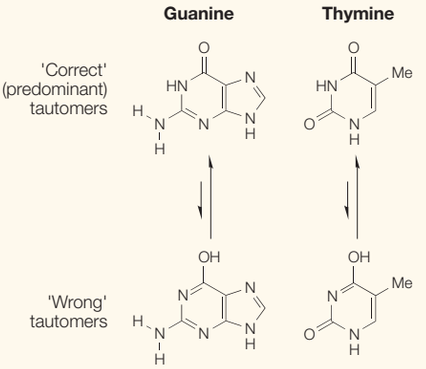
Many different virtual screening (VS) approaches are in use, and researchers often claim that their specific method is the best one. Although some really are more powerful and faster than others, success in research will not so much depend on the specific technique used, but on a proper description of the relevant molecular properties. A very common misunderstanding is that molecules that possess drug-like properties and fulfil the Lipinski conditions[5,15] are automatically 'drug-like' (which has never been proposed by Lipinski himself). Many organic chemicals conform to these rules, but they are by no means drug-like: the 'rule of five' defines only some necessary conditions for a drug candidate, not sufficient ones. 'Drug-like' or 'non-drug-like' character should be decided by other methods, for example, by neural nets[16,17], which (additionally) consider structural features.

As lead structures, in their optimization to drug candidates, often become large and lipophilic, it has been recommended to start the search for new drugs with small and polar compounds[18–20] and with compounds of low complexity, or even from molecular fragments[21,22]. All such recommendations, as valuable as they are, should not be overemphasized, especially in the screening of natural products (as already discussed in REF. 21). There are many examples in the literature in which small drugs resulted from a larger lead structure; for example, most major analgesics are derived from morphine. Whether a drug does indeed become larger and more lipophilic than its lead depends mainly on the experience, creativity and tenacity of the medicinal chemist — it is not a law of nature. Indeed, an inspection of 470 lead–drug pairs showed that the average molecular mass increase from a lead to the final drug was only 38 Da (63 Da for the 78% drugs that had a higher molecular mass than their original lead)[21].

In addition to the Lipinski rules of drug-like properties, and neural nets for the definition of drug-like character, some other filtering techniques are commonly used, for example, to eliminate undesirable atoms or groups (so-called 'garbage filters') and compounds with potential to be cytotoxic. But the question is: to what extent is cytotoxicity related to acute and chronic toxicity, and to what extent can it predict rare toxic side effects? Global *in silico* filters for toxicity or carcinogenicity should be

Box 1 | **Watson, Crick and the wrong tautomeric formulas**[28–31]

**In 1952, the biologist James Watson and the physicist Francis Crick attempted to derive a structural model for DNA. When Erwin Chargaff, a biochemist, visited them in the summer of that year, he was annoyed that neither Crick nor Watson were interested in the chemical structures of the four nucleic bases; both told him that they would look up these structures in a textbook, if needed. Later, they consulted J. N. Davidson's *The Biochemistry of Nucleic Acids*, published in 1950. However, as with other books of that time, it contained incorrect tautomers of guanine and thymine (see figure). Early in 1953, Linus Pauling published a DNA model with the phosphate backbone in the core of a three-chain model. In contrast to this model, Watson and Crick increased their efforts to come up with a helical model with the bases inside. But no matter how they tried, the purines and pyrimidines did not form a nice hydrogen-bonding pattern, as for example, in the protein backbone of an α-helix. On February 27, the theoretical chemist Jerry Donohue looked at their base structures and realized that these were wrong. Starting from the correct tautomers, the key features of the three-dimensional structure of DNA could be fixed the very next morning! On February 28, 1953, the correct double helix structure of DNA, with two strands running in opposite directions, was formulated by Watson and Crick. It was published in *Nature*, on April 25, 1953.**




considered and validated with great care and suspicion; there are too many different mechanisms to fit just one predictive model. In addition, rates of 60% or even 70% correct predictions look fine, but one has to consider that flipping a coin would already produce a 'success rate' of about 50%. In the first case, there would be a 30–40% probability of error in the prediction of a certain property of a compound; in the latter case, a 50% probability, which does not constitute an important difference! If such prediction tools are nevertheless applied , they should only be used to score groups of compounds, not to decide the fate of individual candidates.

## What are the problems in VS?

Pharmacophore analyses and docking are powerful techniques in rational drug design, but they are often applied in an inadequate manner. Whenever people turn on the computer, they are tempted to switch off their brain at the same time, relying too much on some intelligence within the (commercial) programs. Most computer programs accept chemical structures as they are imported by the user. Alternatively, they define donor and acceptor properties of heteroatoms in a very crude manner, without considering the dissociation of acids and ionization of bases, which convert donors into acceptors and *vice versa*, and without considering different protomers or tautomers. Whereas such flaws might be insignificant in the case of the Lipinski rules, they will produce serious errors in structure superpositions, in similarity searches and in docking; wrong tautomers might have even delayed the discovery of the double-helix structure of DNA (BOX 1).

Most important is the correct attribution of the pharmacophore properties of certain atom types. Many people believe that ester groups have two acceptor positions because there are two oxygen atoms. Whereas two is correct for the number of acceptor functionalities, this number results from the two electron lone pairs at the $sp^2$ (double-bonded) oxygen; the $sp^3$ (single-bonded) oxygen is not an acceptor[23]. The nitrogen atoms of oxazoles, isoxazoles and related heterocycles are hydrogen-bond acceptors, whereas the oxygen atoms are not, or are only very weak, acceptors[24]. The oxygen atom in aliphatic and cyclo-aliphatic ethers is a strong acceptor (accommodating two donor groups) but it is a much weaker acceptor in mixed aromatic–aliphatic ethers, and it has no acceptor capability at all in aromatic–aromatic ethers. This is reflected by lipophilicity: the differences in experimental octanol/water partition coefficients are 2.5 log units for the pair pentane/diethyl ether, 1.2 for the pair ethylbenzene/anisole and about zero for the pair diphenylmethane/diphenyl ether (in all cases a $–CH_2–$ group is replaced by –O–)[25]. Wrong donor and acceptor property assignments to certain functionalities will produce poor results in pharmacophore searches and in the docking of ligands into three-dimensional protein structures. Further problems result from the complexity of the binding process: entropic and enthalpic factors act together, inserted water molecules can have a significant role, and ligand and binding-site flexibility additionally complicate the quantitative description — that is, a prediction of binding affinities.

## What's wrong, and could we do better?

It has been commented that the pharmaceutical industry is going to lose individuality, commitment to science, and cultural and ethical standards[2]. We perform high- and higher-throughput research *in vitro* and *in silico*, often neglecting the important *in cerebro* component of drug research. We are not yet living in Castalia: our games are relatively crude, instead of being highly sophisticated. Sometimes, we behave like lemmings in the fog, running behind every new concept or method whether it is validated or not. We rely on artificial *in vitro* systems, hoping that the information from bits and pieces holds true for the whole system. We lose our expertise in classical medicinal chemistry and pharmacology. We do not systematically preserve the precious knowledge gained in past drug discovery projects. As a consequence, we derive strategic decisions from a small and often misleading fraction of the available information.

Is there a way out? Yes, indeed there is: real innovation needs scientists in a stimulating environment. We should counteract the replacement of individual innovation by technical teams. Instead, the teams should provide a proper platform for individuals, who make or contribute to an invention. To maintain the stimulus, there should be a balance between a book-keeping type of research management and freedom for creativity. We should carefully inspect all hypotheses and results, whether they really support our decisions or whether they tell us just the opposite. Many scientists within drug discovery research are aware of these caveats. So, the perhaps trivial conclusion must be that we should not follow false prophecies, but direct our efforts towards serious science, eliminating the myths and reducing the hype. Future success depends on the proper integration of new promising technologies with the experience[26] and strategies[27] of classical medicinal chemistry.

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**Hugo Kubinyi's website:** http://home.t-online.de/home/kubinyi
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OPINION

# Understanding 'Global' Systems Biology: Metabonomics and the Continuum of Metabolism

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To apply genomic knowledge effectively in drug discovery, mechanistic connectivities between genetic variation and disease processes need to be established via systems biology approaches. Humans have hundreds of functionally specialized cell types that interact differentially with environmental factors to influence disease development and to modulate the effects of drugs. Metabonomics can provide a means of modelling these interactions, but the relationships between 'endogenous' metabolic processes (coded in the genome and intrinsic to cellular function) and 'xenobiotic' (foreign compound) metabolism are poorly understood, especially with respect to environmental factors. We present an overview of 'global' mammalian metabolic conversions that should be accounted for in human systems biology models and propose a new probabilistic approach to help understand gene–disease relationships and vexed issues of idiosyncratic drug toxicity.

Systems biology — that is, the computational integration of data generated by the suite of genetic, transcriptomic, proteomic and metabonomic platforms to understand function through different levels of biomolecular organization — offers exciting new prospects for determining the causes of human disease and finding possible cures[1]. Certainly the judicious use of 'omics' data should give new insights and opportunities for the drug discovery and development process and for understanding drug toxicology[2]. From a modelling point of view, considerable advances have been made in correlating gene–protein–metabolite interactions in microorganisms in which linked processes in single cell types can be probed in depth[3]. But even in such simple systems, statistical relationships between, for instance, gene expression and protein levels can be weak[4].

We have argued that the multivariate temporal modelling of metabolism and physiological processes following pathophysiological stimuli can be important in connecting molecular events at the gene and protein level to those occurring at the macrosystem level, including pathological end-points[5–8]. This is likely to be true because changes in the kinetics of specific pathways in cells, tissues and organs are real end-points in their own right. However, there are limitations in the way in which 'omics' data types can be modelled in higher animals, because of the number and spatial dispersion of the interacting cell types. Furthermore, gene expression and proteomic data might only indicate the *potential* for pathophysiological effects, because many pathway feedback mechanisms are simply not reflected in protein concentration or gene expression changes. This realization has led to increased efforts by pharmaceutical companies to try to model transcriptomic and proteomic data in relation to metabolic pathway activity, and to map such data onto well-known pathway databases, such as those provided by the Kyoto Encyclopedia of Genes and Genomes (KEGG)[9]. However, the humanbiological 'system' is very extensive, and the functional integrity of human physiology is also dependent on many external factors, even including other genomes from