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Addressing toxicity risk when designing and selecting compounds in early drug discovery

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Prioritising compounds with a lower chance of causing toxicity, early in the drug discovery process, would help to address the high attrition rate in pharmaceutical R&D. Expert knowledge-based prediction of toxicity can alert chemists if their proposed compounds are likely to have an increased likelihood of causing toxicity. We will discuss how multiparameter optimisation approaches can be used to balance the potential for toxicity with other properties required in a high-quality candidate drug, giving appropriate weight to the alert in the selection of compounds. Furthermore, we will describe how information about the region of a compound that triggers a toxicity alert can be interactively visualised to guide the modification of a compound to reduce the likelihood of toxicity.

Introduction

Toxicity of drugs and clinical candidates remains a significant issue for the pharmaceutical industry, leading to increased attrition and cost, late-stage failures and market withdrawals. Recent data from CMR-International [1] indicate that 22% of drug candidates entering clinical development in the period 2006–2010 failed owing to nonclinical toxicology or clinical safety issues. In preclinical development, toxicity and safety issues accounted for 54% of failures (18% of all preclinical candidates). These expensive late-stage failures account for a large proportion of the cost of pharmaceutical R&D, recently estimated to be US$1.8 billion per marketed drug [2].

For many marketed drugs, toxicity remains an issue, causing adverse drug reactions (ADRs) and leading to black-box warnings, restrictions on use and even withdrawals. These dramatically reduce or even eliminate the return on R&D and marketing investments and harm the reputation of pharmaceutical companies and the industry as a whole. A study by Lasser *et al.* [3] indicates that, of 548 new chemical entities approved by the FDA between 1975 and 2000, 10.2% acquired one or more black-box warnings and 2.9% were withdrawn. Recent, high-profile examples of market withdrawals include cerivastatin (2001), valdecoxib (2005, USA) and rosiglitazone (2010, Europe). Of particular concern are idiosyncratic ADRs that, owing to their rare occurrence, are unlikely to be detected during clinical trials.

From the sobering statistics above, it is clear that addressing failures due to toxicity would have a dramatic effect on the productivity of pharmaceutical R&D and the quality of the resulting drugs. Some toxicity is driven by the biological mechanism of the intended pharmacological action of a compound, particularly in the case of compounds intended for new targets for which the association with a therapeutic indication has not yet been validated. However, a significant proportion of observed toxicities are caused by unintended effects unrelated to the primary biological target. In the latter cases, it should be possible to reduce risk by focusing on structural motifs that are less likely to cause toxicity due to known mechanisms. Alternatively, if a likelihood of toxicity being observed in the clinic can be identified early in the process, *in vitro* or *in vivo* experiments can be prioritised to assess this risk before additional, downstream investments are made.

In the mid-1990s, a similar observation was made regarding a high rate of failure as a result of poor compound pharmacokinetics (PK) in clinical trials [4]. This led to the introduction of *in vitro* assays for high-throughput measurement of ADME properties in early drug discovery [5] and development of computational, or *in silico*, methods for the estimation of these properties [6,7]. The result has been a reduction in the proportion of clinical failures as a result of PK issues from an estimated 39% in 1991

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to approximately 10% in 2000 [8]. Unfortunately, during the same period, the overall failure rate was unchanged and the proportion of clinical failures attributed to toxicity or safety issues increased from approximately 14% to 30%. This, in turn, has motivated a recent trend in developing and introducing *in vitro* assays earlier in the drug discovery process, to identify potentially toxic compounds and halt their progression. Similarly, *in silico* methods for the prediction of toxicity can help to guide the design and selection of compounds with reduced risk of toxicity.

This article will focus on knowledge-based methods for prediction of toxicity (also described as rule-based) that produce a semi-quantitative estimate of toxicity hazards, based on experimental precedence for similar compounds. A number of expert systems have been developed that provide a rule-based approach to toxicity [9]. Other approaches, broadly described as statistical methods, rely on fitting a mathematical model of compound characteristics to empirical data using a variety of techniques including Support Vector Machines, Naive Bayes, Decision Trees and Random Forest [10–14]. The output from knowledge-based and statistical methods is the classification of compounds as toxic or otherwise or predictions of a numerical measure of toxicity (e.g. LD_{50}). The principles that we discuss herein for the application of *in silico* methods to address toxicity in early drug discovery can apply equally to both approaches.

In the following sections we will describe the principles of knowledge-based prediction of toxicity and the challenges posed by application in early drug discovery. We will discuss how these methods can be applied to the selection of compounds, giving appropriate weight to predictions of toxicity against other important factors, and provide feedback on strategies for redesign of drug candidates to reduce toxicity risk. Finally, we will present two applications of knowledge-based toxicity predictions – one for recently approved drugs and the other in the context of a hypothetical hit-to-lead project – before drawing some conclusions.

Knowledge-based prediction of compound toxicity

Expert knowledge-based predictive systems for small molecules are designed to emulate the decision-making process of a group of experts by applying a form of artificial intelligence whereby a knowledge base of facts is used to make a prediction by inferring relationships between facts through a process known as reasoning [15,16]. This enables the introduction of associated data such as reactivity or knowledge of the mechanism of action, and can cope with uncertainty and conflicting data that are common in the field of toxicity prediction. By contrast, purely statistical approaches derive probabilities of toxicity by taking a dataset of compounds, identifying descriptors that show a correlation to activity and use this to predict the toxicity of novel compounds. Statistical systems have the advantage of being fast to implement and can more efficiently cope with large datasets when the endpoint is relatively simple. Expert systems are particularly well suited to making predictions for toxicities derived through multiple mechanisms for which only incomplete datasets are available. Expert systems can often provide more interpretable predictions with detailed supporting documentation [9,17].

In silico systems in the field of toxicity typically predict hazard – the possibility of a chemical causing harm [18]. Expert systems frequently also provide an indication of the likelihood for the prediction to be correct, supporting evidence and a reasoned argument for the cause of the hazard, which might include an expert analysis, a mechanistic explanation or even an adverse outcome pathway (AOP) [19]. Although valuable, such predictions normally require further analysis to derive the risk – the probability of that toxicity being observed. A key part of that analysis is to determine the exposure of the chemical at the site of toxicity – a step that requires an understanding of the dosing regimen, the pharmacokinetics and potentially relevant biological details such as species, age, disease state, sex and the potential for drug–drug interactions. This means that a hazard prediction has to be considered in the context of a number of other factors to derive an assessment of risk.

BOX 1

Examples of the reasoning levels within Derek and their definitions

Certain	The proposition (prediction) is known to be true
Probable	There is at least one strong argument for the proposition and none against it
Plausible	The weight of evidence supports the proposition
Equivocal	There is an equal weight of evidence for and against the proposition

The Derek prediction engine (http://www.lhasalimited.org/) [20], applied in the examples below, provides a prediction (active/inactive) for each toxicity endpoint. If no evidence of toxicity has been found then 'No report' (nothing to report) is returned. A prediction of activity is typically associated with a structural alert, identifying the motif triggering the positive prediction, along with an associated likelihood. The likelihood qualifies this prediction; some of the likelihoods relating to positive predictions are shown in Box 1. In practise, it has been demonstrated that likelihood can be taken as a level of confidence because it correlates well with the accuracy of a prediction [21].

Expert systems are frequently applied in the later stages of drug development [22,23], where it might be necessary to produce an assessment of risk suitable for regulatory acceptance or to design *in vivo* studies that should be undertaken to support a submission. In such cases, features including mechanistic interpretation, expert commentary, documentation, performance statistics and supporting data are particularly valuable. At this stage of the process, relatively few compounds are assessed for toxicity and the endpoints can be relatively complex, meaning that training sets for *in silico* models tend to be sparse and do not always sufficiently capture the different mechanistic pathways at work. To overcome this, collaborative data sharing, through organisations such as Lhasa Limited, enables participating companies to gain knowledge of toxicities from proprietary data without revealing confidential information such as biological targets or chemical structures.

By contrast, these methods have been less commonly applied in early drug discovery, where the numbers of compounds considered are much larger and the scientists using the predictions are less likely to be expert toxicologists. This makes detailed examination of each prediction, using detailed supporting information,

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