

The New Science of Predictive Safety Testing

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What price would a company pay to know that a compound in development had potential safety issues? New approaches to predictive safety aim to consider the whole complexity of human cellular biology by integrating all the available data, and ‘learning’ and reproducing the real behaviour of the system – the human body – using mathematical models.

How much would you pay for an airbag five seconds before crashing into a tree? Certainly tens or hundreds of times the price of the airbag itself. How much would you have paid if somebody could have predicted the safety profile of your drug before you realising – once recovered from the shock – that the results of your Phase 3 trial showed potential safety issues, and thus all your clinical development was jeopardised and potentially millions of dollars wasted?

Although these might seem like rhetorical questions, we believe that they are not. Over the last 10 years, dozens of ready-to-market or already marketed drugs have been withdrawn after exhibiting unexpected severe adverse events (AEs) – some of the more prominent examples being rofecoxib (Merck & Co), torcetrapib (Pfizer) and rimonabant (Sanofi-aventis). The major causes of attrition in the clinic are lack of efficacy (accounting for approximately 30 per cent of failures) and safety (toxicology and clinical safety accounting for approximately a further 30 per cent) (1). Could these failures have been avoided? We will never know – but we believe that the pharmaceutical industry and regulatory agencies should make all the efforts necessary to prevent the catastrophic consequences of such failures (as many are already doing) – just as the car industry invests in the best airbags and car-stability controls to reduce the risk of accidents. Identifying potential toxicity issues early in the drug discovery process can save time and money that would otherwise have been wasted on continued compound development. Even more importantly, it could protect patients from being exposed to unnecessary risks.

A PARADIGM CHANGE

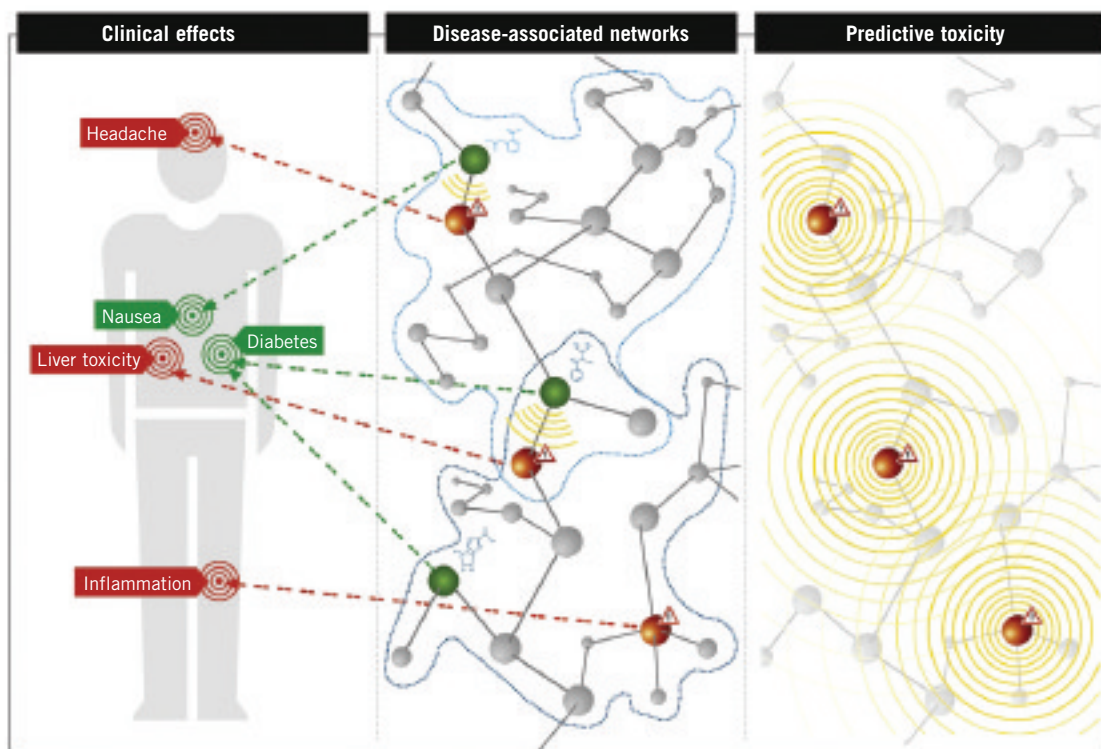
Traditionally, preclinical safety pharmacology efforts to predict AEs during the early stages of drug discovery

involved testing molecules by using *in vitro* biochemical and cellular assays – that is, by testing the direct binding of the drug to the molecular site in the body (normally a protein) that elicited the physiological reaction responsible for causing the AE. But this approach only works well when the following two premises are met: 1) the AE has a well-characterised effector; and 2) activation of the effector can be analysed by an *in vitro* analysis (for example, an *in vitro* binding test). Some adverse event effectors fall into this category; for example, the cardiovascular drugs terazosin and prazosin cause dry mouth due to their effects on salivary gland alpha1-adrenoreceptors (2).

But in the reality of the human body, these two conditions are rarely met. Often, AEs occur by mechanisms that seem not to be directly linked to the action of the drug primary target; or in many other cases, the target profile of the drug under study is not well known and characterised. Actually, the fact that similar side effects of unrelated drugs can be caused by their common off-target actions has been exploited to infer the molecular activities of those drugs that are not implicit in their chemical similarity or the sequence similarity of their known targets (3). Apart from giving insights into the molecular basis of a drug’s side effects, this approach provides a way to identify additional hidden targets with potential use in different therapeutic categories.

NEW APPROACHES TO PREDICTIVE SAFETY

Nowadays, there are innovative ways to detect early signals that something might go wrong. New approaches to predictive safety have a key component in common: they exclude the hypothesis that we are dealing with simple, linear, ‘electric circuit-like’ systems, but instead are having to deal with hyper-complex, blurry,



Source: Trends in Pharmaceutical Sciences (8)

redundant, mostly unknown systems that – surprisingly – happen to work quite well (so that we can be alive). These new approaches – encompassed in the global term ‘Systems Biology’ – try to consider the whole complexity of human cellular biology by integrating all available data, and ‘learning’ and reproducing the real behaviour of the system (the human body) by using mathematical models. The current and future availability of extensive chemical repositories – such as DrugBank, PubChem, KEGG, ChemSpider and others – that include relationships between molecules, targets, adverse events and pathways are key pieces of this new paradigm (4,5).

Figure 1: Network biology applied to predictive safety

The disease-associated networks for diabetes (dark-blue dotted lines) and nausea (light-blue dotted lines) contain several proteins that have been reported to be likely to cause some frequent adverse effects if their normal functioning is affected (red nodes). In addition, the networks contain drug targets annotated to a specific disease (green nodes).

Models that can identify the areas of influence of proteins leading to undesired effects are created; these help to identify potential drug targets that are likely to trigger severe adverse reactions in the early stages of the discovery process, and to design rationally the toxicity tests needed to check the safety of other drug targets under the area of influence of a certain red node. Also, a detailed description of the molecular networks associated with certain diseases can highlight the existence of validated drug targets for a given therapeutic indication in key enclaves of the network describing a different disease, thereby suggesting candidates for drug repurposing – that is, finding new indications for a target.

For instance, the so called ‘Systems Chemical Biology’, as published by Scheiber *et al*, combines knowledge-based annotation of AEs to chemical structures and knowledge-based annotation of pathways (6). With this approach, the fact that often-dissimilar chemotypes show the same side effects has also been exploited; but in this case, they integrate a well-established cheminformatics target prediction method with systems biology data. This analysis is based on the hypothesis that these compounds hit different targets in the same pathway and thereby cause the same phenotypic effect. Besides the application of this method in safety prediction, its use can also be envisaged as a ‘compound triage’ and as a design tool to engineer desired properties into compounds.

Another approach, as published by Aloy *et al*, is based on creating predictive models based on the relationship between key proteins for the condition to be treated, drug targets and AE ‘motives’ (pathophysiological causes) (7). Combining these complementary pieces of information, with each one able to reveal different aspects of the system, it is possible to identify potential toxicity issues.

STEPS IN THE PROCESS

In the first place, a detailed map is built around the identified drug targets – predicted either experimentally or computationally – by using all known protein-protein

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interactions. A key step in the process is the construction of a database of adverse event motives. The final effector proteins responsible for causing the AEs are identified by extensive literature review procedures and grouped by motive. With this approach, the motives offer a clear advantage with respect to 'pathways', as they are more focused on the final results – that is, whether or not a given adverse event is produced. A model is created by using artificial intelligence techniques and validated on the basis of available experimental data.

Perturbation of the system finally allows relationships between drug targets and undesired effects to be

unveiled. Chemical toxicities are predicted by considering the physical or functional proximity of a given compound in a network, as well as the proteins known to cause some undesired side effects if their function is affected (see Figure 1, page 57).

POST-HOC SITUATIONS

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