Predicting human safety: screening and computational approaches

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Current preclinical safety evaluation programs use a combination of computational methods, mechanistic *in vitro* screening and – primarily – *in vivo* experimentation to predict human toxicity. The rapid transition of pharmaceutical R&D into electronic R&D (e-R&D) makes it imperative that predictive safety testing also develops into an information-rich, knowledge-based process in the near future. Accordingly, enhanced databases and computational tools are expected to change the way the pharmaceutical industry assesses drug toxicity during discovery and early development. Expert use of prediction tools should lead to lower failure rates in drug development and decrease the cost and time involved in successful drug approval.

Since the 1970s, the number of successful drugs reaching registration has remained fairly constant: one-tenth of compounds in investigational new drug (IND) development phases are eventually approved for use[1]. However, the costs of developing drugs at least tripled from the 1970s and 1980s to the 1990s. While productivity at the research end has soared – from 1990 to 1997 the average annual number of samples processed per scientist increased from 75,000 to 2.5 million (Ref. 2) – the failure rate in early and late stage development remains alarmingly high[3]. The cost of late failures in both dollars and time can neutralize the economies gained by highly productive research engines. A high proportion of early and late pipeline dropouts occur because of undesired toxicity[4]. Established preclinical paradigms for predicting clinical outcome are only partially successful and must be examined continually and, eventually, replaced by new technologies for discovering biomarkers of toxicity, higher-throughput screening to develop relevant databases and both computational and simulation approaches to predict safety[5,6]. This review examines some newer approaches currently in use within the pharmaceutical industry and highlights the gaps that remain in our knowledge and ability to bring these new technologies into general use within safety assessment.

Reasons for safety-related dropouts in development

Almost one-half of the drug failures in investigational drug development phases are because of unacceptable efficacy (which includes suboptimal pharmacokinetics) and approximately one-third (in two reviews, 27–40%) because of safety issues[3,7]. When drugs fail because of toxicity, it is usually for one of four reasons:

- Toxicity seen in animals (or *in vitro* systems) is not fully understood, therefore the potential risk to humans cannot be estimated or, by default, tolerated
- Toxicity seen in animals (or *in vitro* systems) is understood, the relevance to humans is known or suspected, and the potential risk to humans is considered unacceptable
- Acceptable therapeutic margins (between efficacy and toxicity) cannot be established in animals and/or humans
- Studies in animals did not predict human toxicity seen in clinical trials.

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The goal of predictive safety testing, screening or computation/simulation is to resolve these issues as early in the discovery or early development process as possible. For instance, if certain potential toxicities could be associated with chemical structure, it seems feasible that filtering could take place during the design of chemical libraries. Confirming assays could then be incorporated into secondary screens as gating criteria during lead optimization. It is to be hoped that these practices become the operative form of preclinical safety assessment in the future.

Safety evaluation in the discovery–development interface

The crucial stage of development when compounds are optimized, enter (so-called) predictive preclinical models and are tested in early clinical trials has been called the discovery–development interface (DDI)[1,3]. The transition from the DDI, as viewed today, to a 'virtual discovery–development interface' (e-DDI) of the future is highlighted in Figs 1, 2 and 3 (Johnson, D. e-DDI: The virtual discovery-development interface. *219th ACS National Meeting*, 26–30 March 2000, San Francisco, CA, USA, abstract CINF 0022). The concept of being able to use information as a primary tool and to supplement it by testing (the e-DDI paradigm) is already emerging within the pharmaceutical industry. It has been estimated that, by 2005, only companies that have invested in the emerging *in silico* (e.g. computational) technologies and cyber-business opportunities, have learned to mine the information they contain and made the transition to e-R&D, will be able to function properly[8]. These predictions are as directly applicable to preclinical safety evaluation as they are to any functional area within R&D.

Figure 1 depicts the current state of the DDI, where screening groups have been assembled to incorporate 'corrective' pharmaceutical properties into compounds as part of the hit-to-lead and lead optimization steps. It has been estimated, but not proven, that the 65% dropout rate (from declaring a lead as a development candidate through to Phase I) exists today despite new DDI screening. However, benefits are expected to accrue in the near future. Fig. 2 shows the interim state of developing relevant databases, either from public or internal sources, while Fig. 3 depicts an operational information-based learning process. Today, we find ourselves in a transition state, somewhere between Figs 1 and 3. The absorption, distribution, metabolism and excretion (ADME) portion of the DDI is moving rapidly into a higher-throughput mode, concentrating on rank-ordering compounds in a chemical series to select leads with optimal bioavailability and exposure characteristics. The toxicology portion of the DDI is currently focused on discovering new biomarkers of toxicity – which might lead to higher-throughput screening – and the development of datasets that can be used with predictive, computational tools.

Current screening and computational approaches

Increased throughput and/or miniaturization of assays – to match discovery throughput

The goal of this approach is to identify the crucial area where the bottleneck exists and to remove it as a rate-limiting

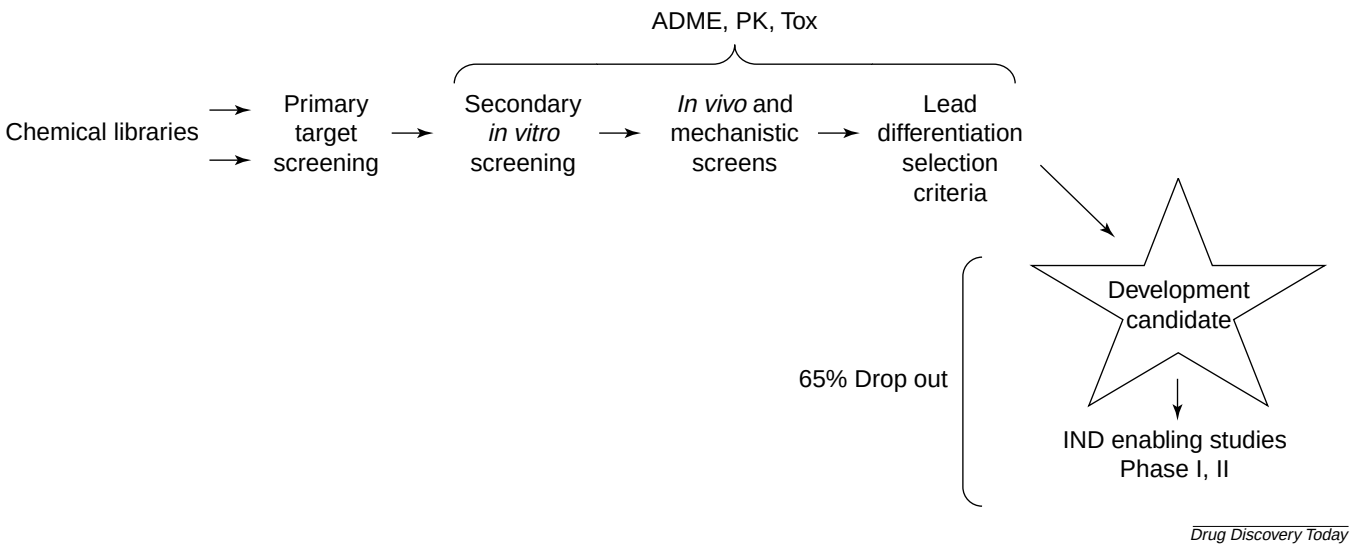

Figure 1. *The current drug–development interface (DDI).*

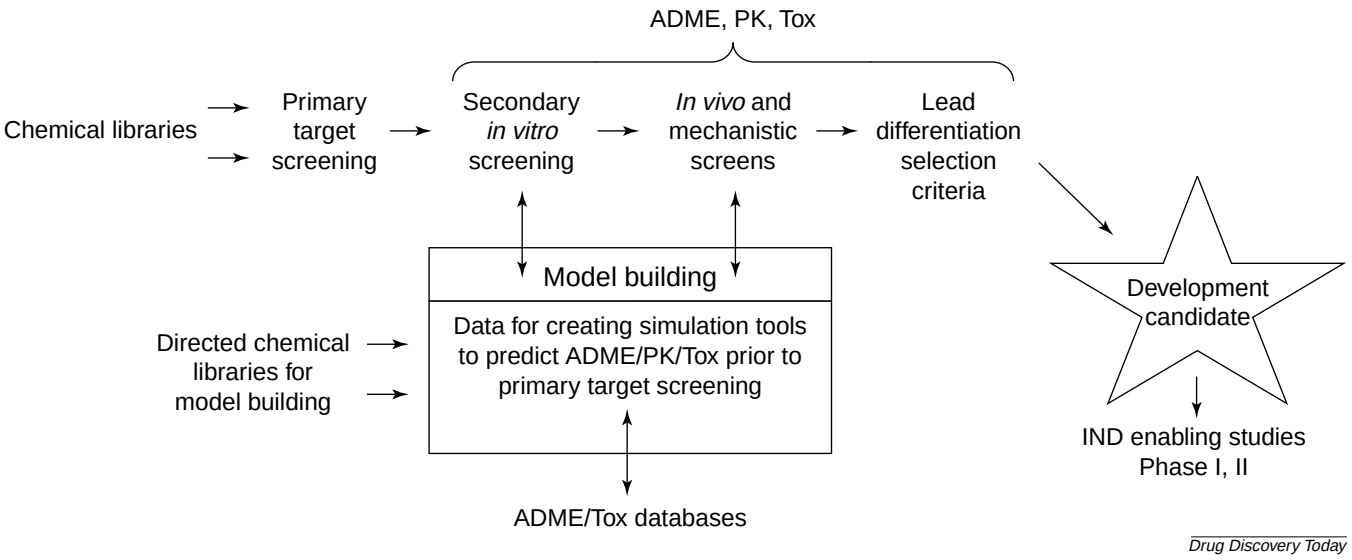

Figure 2. *The early phase of virtual drug–development interface (e-DDI): developing relevant databases.*

step[9–13]. A good example is the desire to determine relative oral bioavailability early in the lead generation process where the rate-limiting step is usually bioanalytical resources. Protocols have been designed for N-in-1 (number of compounds in pool) experiments where cassette (pooling of multiple compounds) dosing[13] or analysis[14] takes place. Interactions must be taken into consideration with either approach, but particularly when dosing pooled samples. Another approach for rapid pharmacokinetic screening is to determine an estimated area under the curve (AUC; systemic exposure over time) by pooling repeat plasma samples to determine a single average concentration[15]. Both examples result in a significant reduction in bioanalytical resources and enable a rapid 'rank-ordering' of compounds with more desirable characteristics. As efficacy or toxicity is dependent on

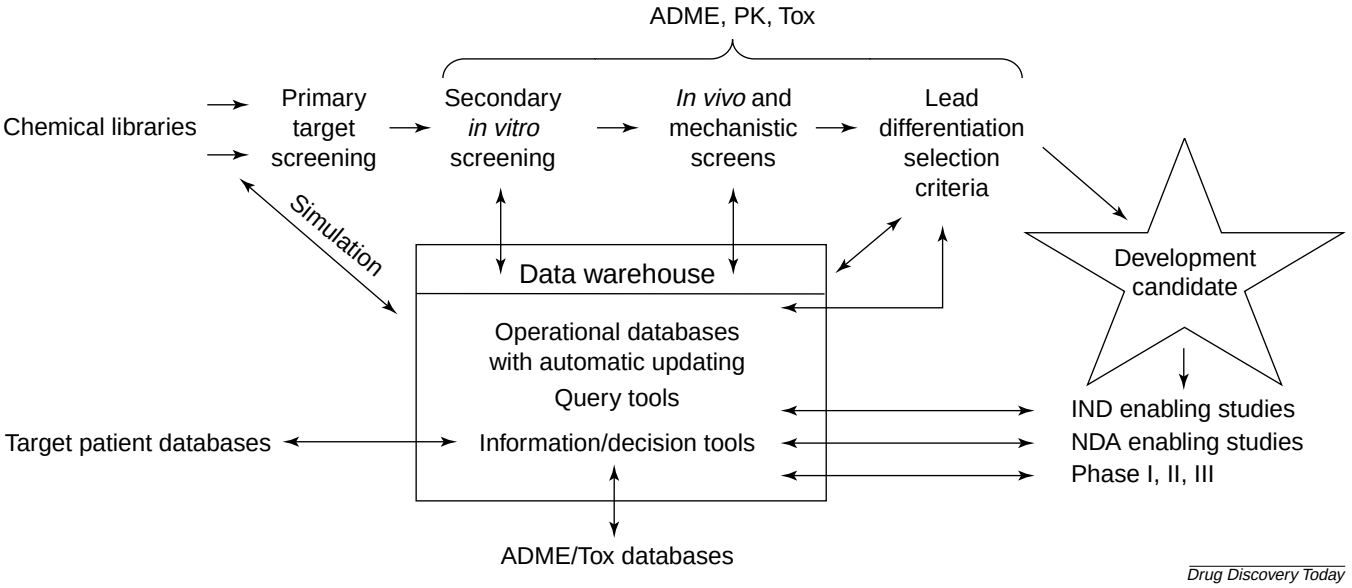

Figure 3. *Fully operational virtual drug–development interface (e-DDI): databases with effective query and predictive tools.*

exposure, these determinations can speed the entry into more relevant *in vivo* testing. Specific tests for safety have been incorporated at this level, particularly genotoxicity and cytotoxicity in different cell lines representing potential target organs. Assays and new products have been discussed at recent meetings on ADME/Tox screening and are amenable to HTS. The two mentioned here as examples have undergone some level of validation against specific subsets of chemicals (including drugs), although their use is not endorsed by their inclusion in this article. Vitotox™ (Labsystems OY, Helsinki, Finland) is a bioluminescent genotoxicity and cytotoxicity test, based on *Salmonella typhimurium*, carrying a *Vibrio fisheri* luciferase operon under the control of the SOS regulatory network (Lampinen, J. Screening compounds for genotoxicity and cytotoxicity: an SOS bioluminescence *Salmonella typhimurium* test to measure genotoxicity kinetics. *Predictive toxicology in drug discovery*, 10–11 November 1999, New Orleans, LA, USA). The assay, in 96- or 384-well format, detects DNA damage, gene mutations and cytotoxic effects simultaneously. Veragenics (Vancouver, BC, Canada) has developed an *in vitro* test for identifying carcinogens using a bovine papillomavirus DNA-carrying C3H/10T1/2 mouse embryo fibroblast cell line (Kowalski, L.A. *et al.* *In vitro* prediction of carcinogenicity using a bovine papillomavirus DNA-carrying C3H/10T1/2 cell line (T1). *Predictive toxicology in drug discovery*, 10–11 November 1999, New Orleans, LA, USA). Validation has been done against 100 chemicals including steroids, antineoplastics, polycholorinated biphenyls (PCBs), dioxins, alkyl halides, aromatic amines, nitrogen heterocycles, polyaromatic hydrocarbons, mustards and benzodioxoles. As with all new assays, validation against sets of pharmaceutical compounds with known outcome (both negative and positive) is essential; however, at the screening stage, it might be more important to focus on rank-ordering of compounds rather than clear cut decisions.

Creating alerts or filters to narrow the scope of lead generation

The most widely used example predicts that poor absorption or permeation (hence poor bioavailability) are more likely when a chemical (for example, a lead compound) has more than five hydrogen-bond donors (expressed as the sum of hydroxyl and amine groups), the MW is >500, the log P (measure of lipophilicity) is >5, and there are more than ten hydrogen-bond acceptors (expressed as the sum of nitrogen and oxygen atoms)[16]. Some companies will not synthesize compounds that surpass two or more of these gating parameters; other companies categorize compounds into strata of 'poor' performers to 'good' performers, based on the outcome of screening results. 'Good' performers tend to have an aqueous solubility >0.1 mg ml^{-1}, Caco-2 permeability >1.0 × 10^{-6} cm s^{-1} or human hepatocyte stability of >50% (Ref. 4). The most commonly used filters for safety are alerts generated by computational tools for genotoxicity and potential carcinogenicity.

Mechanism-based predictive in vitro *assays*

The most widely used mechanism-based predictive assays are genotoxicity assays to predict animal (and, by extension, human) carcinogenicity, *in vitro* metabolism assays to predict human pharmacokinetic parameters and prediction of potential drug–drug interactions using hepatocytes or cDNA-expressed cytochrome P450 isozymes[14,17–24].

Specific target organ toxicity assays (cells or slices) are typically used when a specific mechanism of toxicity has been elucidated. The assay is then used as a secondary screen within an analogue series as part of the optimization step. Because of the lower throughput of these assays, they are generally reserved for later screening in the lead selection step. For the pharmaceutical industry today, this represents a bottleneck in the hit-to-lead process of discovery. There are several reasons why this area has not developed as quickly as high-throughput assays for ADME screening; the two most prevalent are the presumed need to validate these assays at the level of replacing *in vivo* studies (an agonizingly slow and time-consuming process) and a concern not to develop any negative data on compounds early in the discovery process, as this might cause trouble later (the head-in-the-sand paradigm). Target organ screening in a high-throughput mode is an area that requires further development and could be key in the future success of DDI approaches.

Computational, QSAR or simulation tools

The most important aspect of computational, quantitative structure–activity relationships (QSAR) or simulation tools is the experimental data that is used to generate rules or QSAR algorithms[25,26]. Several of the datasets are based on older information with no screening information from newer technologies, others contain information sets that are difficult to correlate laboratory-to-laboratory (or publication-to-publication) and still others might rely heavily on a single publication. The most useful computational tools of the future will enable alteration of the rules or updating of the algorithms based on new information in a proprietary mode. e-DDI will rely heavily on expert use of these tools and the databases and analyses must therefore be improved on a continual, but controlled, basis.

Today, the DDI process in most companies is still predominantly empirical (using *in vivo*-generated information compared with archived information). However, it is anticipated that, after being adopted, newer technologies should improve the odds in drug development favorably. The main question as we move forward is just how predictive are the archived *in vivo* animal data, *in vitro* (with *in vivo* correlates) data and the currently used computational tools?

How predictive are current approaches?

In vivo *approaches*

The human predictability of standard animal toxicity tests for pharmaceutical compounds has been assessed by the Health and Environmental Sciences Institute of the International Life Sciences Institute[27,28]. A database has been developed from surveys tabulating significant human toxicities identified during clinical development and determining whether animal toxicities did or did not identify target organ biomarkers for the relevant human toxicities. Results to-date indicate a positive concordance rate for animal models predicting human toxicities of 73% for rodent plus non-rodent species. Prediction rates for non-rodents and rodents alone were 65% and 45%, respectively. This study suggests that animal tests have value in predicting human toxicities, but points out that improved methods are required to reach a high level of confidence. The real coefficient of predictability of *in vivo* studies assessing the full range of the toxicity question (as stated earlier in the four types of failures) is unknown. In some narrowly defined areas, such as cytotoxic agents for cancer therapy, the use of standard rodent and non-rodent tests have – reportedly – been reasonably predictive. Use of the rodent LD_{10} and the dog-toxic-dose-high (a dose that is lethal when doubled) tends to correlate with the human maximum tolerated dose on a mg m^{-2} basis, and dose-limiting toxicities have been predicted with the exception of nausea and vomiting[29,30]. In these examples, the mechanism of toxicity is known and there is little species specificity.

Two high-profile examples of the failure of animals to predict human liver toxicity are fialuridine (FIAU) and troglitazone. Severe and unexpected hepatotoxicity occurred in a Phase II trial of FIAU in chronic hepatitis B patients[31]. This toxicity appeared in seven of 15 patients after several months of dosing; five patients died and two survived following liver transplantation. This observed toxicity, caused by widespread mitochondrial damage, was not predicted by earlier clinical trials or by preclinical testing using conventional laboratory animals[32]. Several important lessons emerged from this incident, not least that the choice of species is crucial to detecting toxicity[32,33] and that an understanding of mechanism (in this case mitochondrial toxicity) can be used to screen for potential toxicities in a class of compounds. Woodchucks chroni cally infected with woodchuck hepatitis virus (WHV) have since been found to be a good model for the efficacy and toxicity of antiviral agents and it has been demonstrated that *in vitro* assays for mitochondrial function can also discriminate between toxic and non-toxic nucleoside analogues[34]. The inability of preclinical research to predict the idiosyncratic liver abnormalities reported with human use of troglitazone[35] has resulted in a series of regulatory actions, a warning label being attached to the entire class of thiazolidinediones, and the eventual removal of troglitazone from the US market[36].

Recent reports on a potent anticancer drug called TRAIL/Apo2L indicate a lack of correlation between results in animals and in human liver tissue[37]. Preclinical studies in mice and non-human primates have shown that TRAIL does not induce substantial systemic toxicity[38,39]. When examined in *in vitro* systems, TRAIL induced apoptosis in target cells (tumor cell lines) and normal human hepatocytes but not in rhesus, rat or mouse hepatocytes. This research suggests that human liver toxicity might result if TRAIL were to be used in experimental human cancer therapy and further preclinical tests are warranted.

In summary, *in vivo* toxicology studies can be predictive of human toxicities but the actual success rate (considering again the four reasons for failure from toxicity) is largely unknown. New biomarkers of toxicity must be found and more relevant animal models must be explored.

In vitro *systems*

Numerous *in vitro* systems were developed and utilized to assess safety and efficacy during the 1980s and 1990s. These tests reduce compound requirements, animal use, time and cost, and in some cases can be amenable to higher-throughput screening. *In vitro* toxicology and ADME tests are routinely used to help select leads from a chemical series and (theoretically) to select candidates for development with a higher probability of success. However, as stated earlier, much of the *in vitro* safety testing has focused on resolving safety issues that arise during drug development, predicting the class-specific toxicity potential and characterizing metabolic profiles. It is hoped that these systems will improve drug design and enable the extrapolation to human outcomes[40]. No definitive study (or survey) defines how successful these approaches have been in industry, with the possible exceptions of genotoxicity and skin and eye irritation.

Investigators have long utilized *in vitro* genotoxicity tests as predictors of carcinogens. Concordance between Ames and other *in vitro* tests with rodent carcinogenicity results range widely depending on the groups of chemical tested, but average around 70% (Ref. 41). Davila *et al.*[40] described the utility of keratinocytes and corneal epithelial models for predicting *in vivo* skin and ocular irritancy. While the datasets are small and skewed towards surfactants, there is a good correlation between *in vitro* and *in vivo* results. Numerous hepatic systems, including microsomes, hepatocytes, genetically engineered cell lines and tissue slices, have been used to examine the mechanism of toxicity as well as the metabolism of pharmaceutical agents (reviewed in Refs 40 and 42). A scheme using hepatocytes as an example of DDI screening approaches is presented in Fig. 4.

Prediction of human pharmacokinetic parameters from *in vitro* metabolism data has been reported extensively. Estimates of human clearance from liver microsomal half-life information can be a suitable predictive approach under a certain set of assumptions and with specific classes of compounds[43]. Considerable progress has been made in establishing *in vitro* systems to evaluate ADME characteristics of compounds[44]. High-throughput approaches are now being applied[12] but the predictive value of ADME screens still falls in the rank-ordering realm of estimation, as little systematic research has been conducted with large compound sets, covering a defined chemical space and with a reliable high-throughput model. The FDA recently evaluated the ability of *in vitro* metabolism to predict and interpret *in vivo* metabolic drug–drug interactions[45]. Successful prediction of clinically significant drug interaction was described with *in vitro* metabolic inhibition data, as were several cases where lack of *in vitro* metabolic inhibition correlated with the absence of a clinical drug–drug interaction. However, there were also cases of non-predictive data (false-negative and false-positive), which highlight the importance of considering the multiplicity of factors associated with *in vivo* drug disposition when interpreting *in vitro* data.

A goal for all of these systems is to demonstrate that the data obtained are valid and can be used reliably in extrapolating from *in vitro* to *in vivo* and from animal to man. While this task alone is daunting, the real challenge is to use the generated datasets to form predictive models for unknown entities.

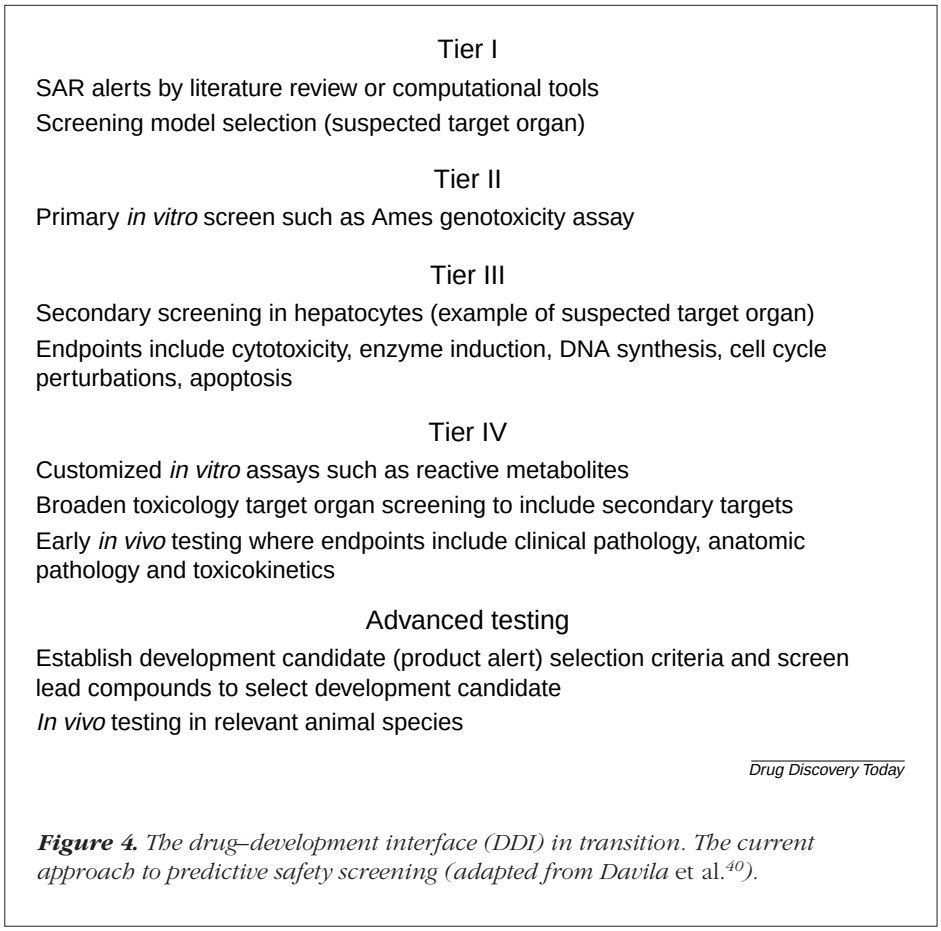

Figure 4. *The drug–development interface (DDI) in transition. The current approach to predictive safety screening (adapted from Davila* et al.[40]*).*

Computational approaches

In silico or computational toxicology seeks to utilize the data generated in *in vitro* and *in vivo* models by evaluating the quality of the data, developing databases, using computer algorithms and statistical approaches to analyze the data (relating chemical and biological data) and establishing predictive capabilities based on QSAR models or toxicity endpoint libraries.

Several computer models and screening tools that are already in use will be described later. Two distinct types of systems have emerged: those based on rules derived from human experts and literature and those relying on statistical approaches (reviewed in Refs 25,46–49). The advantage of rule-based systems is that they are based on an understanding (or hypotheses) of the mechanisms of molecular interactions and can deal with incomplete knowledge (no training set required). However, it is difficult to obtain and prioritize a complete set of rules and, at present, these

systems cannot quantify risk. While statistical or correlative approaches require a training set to generate the structural descriptors and QSAR models, they can quantitate risk and might provide an indicator of the robustness of a prediction. The requirement for a training set means that there is risk in extrapolating outside the class of chemicals described by the model. Statistical models have an advantage in that they can automatically include new 'relationships'; rule-based systems do not enable new relationships without further input from human experts.

Current developments

Some examples of commercial databases that are currently being evaluated and utilized by the pharmaceutical industry for toxicity prediction will be described. These are only selected examples of systems that are currently available for toxicity prediction and do not encompass the wide array of additional toxicology databases, systems for metabolite prediction, and ADME prediction programs.

DEREK (Deductive Estimation of Risk from Existing Knowledge; Lhasa Ltd, Leeds, UK) is a rule-based system that describes the relationship between a toxicophore and its associated toxic effect[50,51]. This mechanistic approach seeks to incorporate molecular properties, biological data and chemical structures into the rules. The database covers a broad range of toxicological endpoints including mutagenicity, carcinogenicity, skin sensitization, reproductive toxicity and neurotoxicity. The latest version of DEREK (version 3.1.1) is Windows-based and can be linked to a metabolite prediction program (METEOR), which enables the user to evaluate the toxic properties of potential metabolites. As DEREK itself cannot generate new rules, the DEREK rulebases are under constant development by Lhasa Ltd and existing users. For instance, DEREK was tested with a set of 250 chemicals from the National Toxicology Program (NTP) mutagenicity database; the system correctly predicted 98% of the 112 Ames-positive compounds and 70% of the 138 Ames-negative compounds[50,52]. In this system the false-positives can be examined and then the rules modified to improve the prediction rate[51]. Barratt and Langowski[53] conducted a similar validation and refinement exercise, testing the sensitization ruleset with 84 contact allergens. The existing rulebase identified toxicophores for skin sensitization in 85% of chemicals, with a refinement of the rules the prediction rate improved to 98%.

TOPKAT (Toxicity Prediction by Komputer Assisted Technology; Oxford Molecular, Hunt Valley, MD, USA) uses quantitative structure–toxicity relationship (QSTR) models for assessing various toxic effects of chemicals from their molecular structure (electrotopological descriptors). Modules containing QSAR models and a database have been constructed to assess a series of toxic endpoints, including rodent carcinogenicity[54], Ames mutagenicity[55], rat oral LD_{50}, rat chronic lowest-observable adverse effect level (LOAEL), developmental toxicity potential and skin sensitization. The interface determines whether new structures are in the optimum prediction space (an indicator of robustness of prediction) and calculates QSTR similarity distance from chemicals with experimental data to assess reliability.

MCASE (Computer Automated Structure Evaluation; MULTICASE, Cleveland, OH, USA) software generates all possible substrates of a defined dimension (two- to ten-atom molecular fragments or biophores) in each compound and finds substructures characteristic of the toxic activity[56,57]. The frequency and statistical significance of each biophore is tabulated to generate structural alerts. Unique to this system is the ability to identify inactivating/deactivating substructures. In collaboration with MULTICASE, the Office of Testing and Research at the FDA has made several enhancements to the standard carcinogenicity database by increasing the size of the dataset, generating separate datasets for male and female rats and mice, adding a scaling factor for potency and improving assay evaluation and acceptance criteria[58]. Beta testing indicated that these enhancements improved coverage from 51% to 94%, predicted many more structural alerts, had excellent predictive value and specificity (97 and 98%, respectively, with only one false-positive) and good concordance (75%). Other databases for acute and chronic toxicity studies, reproductive and developmental studies, genetic toxicology and neurotoxicology are being developed and will be used to develop new MCASE modules[58].

Each predictive system has advantages and disadvantages in coverage of chemical space, quality of the data used to establish rules or models, user-friendliness, throughput for screening and, ultimately, predictive power. While these systems are not yet ideal, they are useful in certain situations and many companies have chosen to use two or more expert systems in parallel to improve predictability.

Conclusions and future perspectives

If the four toxicity issues already mentioned are to be resolved in an e-DDI mode and are to have a favorable effect on cost and time, preclinical safety assessment must move from an experiment-based process to a knowledge-based, predictive process, where experimentation is primarily used to confirm existing knowledge (Woods, J. Mining the discovery data mountain. *Informatics and*

computing support for early ADME and toxicology studies, 18 October 1999, London, UK). The knowledgebase will rely heavily on the quality (and predictability) of older, archived data; continual updates from data generated through both *in vivo* and *in vitro* studies; and future and newly generated information from newer technologies, such as high-throughput toxicity screening, gene and protein expression, metabonomics (metabolic responses to pathophysiological perturbations) and bioinformatics[1]. Eventual success in computational and simulation safety evaluation approaches will also lead to reduced animal use as better lead compounds will emerge into animal testing and reduce the number of undesirable candidates pursued.

Needs for the future

New databases

A gap in our current *in vivo* knowledgebase could affect the utility of future computational approaches. The most extensive datasets in the public domain today are weighted toward 'safer' pharmaceutical compounds and toxic industrial chemicals, while failed or toxic pharmaceutical structures (not making it to the IND stage) usually exist only within individual company archives. Release of this information into the public domain would significantly enhance the field of predictive toxicology. At the same time, new data must be generated to fill the gaps of diversity in chemical structure and space and incorporate new biological marker (of toxicity) information. The process for doing this will require:

- Methodologies that are validated to generate predictive data
- Data that are obtained through broad-based experimentation
- Tools to analyze the data
- Extraction of knowledge by experts.

More specific markers of toxicity

The use of toxicogenomics (particularly microarrays) to assess the mechanism of toxicity has grown dramatically, as evidenced by the large number of abstracts on this topic (>50) presented at the recent Society of Toxicology meeting[59]. It is anticipated that methods such as microarrays, and eventually proteomics, will facilitate rapid toxicity screening while providing more detailed information on mechanisms of action and mechanisms of toxicity[60,61]. Currently, the majority of experience with microarrays and other gene expression technologies is with compounds such as phenobarbital, tetrachlorodibenzo-*p*-dioxin (TCDD) and peroxisome proliferating agents, i.e. compounds of known mechanism for which a vast quantity of data on the *in vivo* responses exists. The possibility that a group or class of compounds might induce signature patterns of gene expression is the basis of applying toxicogenomics to predictive toxicology. The size and quality of the dataset needed to obtain predictive value is as yet undetermined. This area of research is potentially the most exciting in developing an understanding of mechanisms and new biomarkers; it is currently in the validation stage within the pharmaceutical industry.

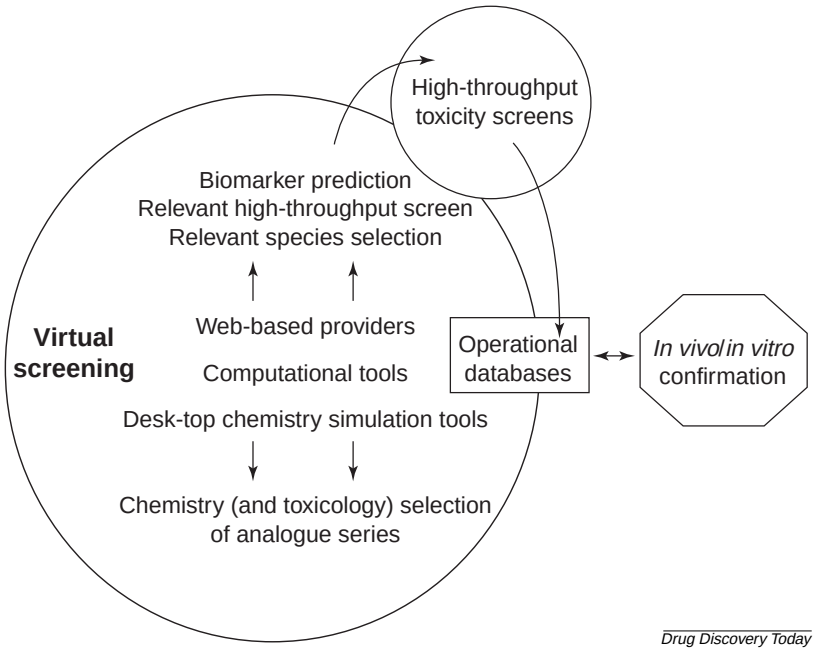

Figure 5. *Predictive safety screening with virtual drug–development interface (e-DDI): a continual loop approach.*

In conclusion, the primary mode of predictive safety evaluation is changing from experimentation to an information- and knowledge-based process. The speed of transition depends on the success of applying new technologies into a better understanding of biomarkers of toxicity and creating relevant databases to enhance computational approaches. Figure 4 shows a composite view of the current predictive safety process within industry[40] depicted as a tier approach. The extent of computational tool usage

varies by company, as does the degree of internal database development. Figure 5 depicts a new 'continual loop' approach where the majority of tier I–III functions are accomplished in a virtual mode. This approach, combined with the rapid transition into confirmatory in vitro and/or in vivo assays, will result in the selection of leads and definition of development candidate criteria and is expected to create an enhanced method for safety prediction in discovery and early development in the future.

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Corrigendum

Please note a correction to the company mentioned in the legend for Fig. 10 in the article *Can peptides be mimicked?* by Nigel R.A. Beeley, published in *Drug Discovery Today* (2000) 5(8), 354–363. The legend should have read:

Figure 10. *A comparison between Hirschmann's sugar-based somatostatin agonists with an early Sandoz (now Novartis, Basel, Switzerland) benzodiazepinone agonist.*

The author would like to apologize for this inaccuracy and for any misunderstandings that this might have caused.

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