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## Omic profiling for drug safety assessment: current trends and public–private partnerships

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The drug development process is currently being hindered by non-optimal prediction of toxicity. Advances in molecular profiling approaches, such as transcriptomics, proteomics and metabolomics, offer the potential to provide a more comprehensive insight into toxicological effects than hitherto possible. These new technologies present their own challenges, however, particularly in relation to standardization and assessment. The focus of this article is on describing the current trends concerning the application of omic approaches in drug safety assessment, with specific emphasis on the role of public–private partnerships in advancing this emerging arena.

### Introduction

Despite huge investment in target and lead compound discovery processes, the number of new drugs entering the market has stagnated. Of those compounds that enter into preclinical development, about 90% currently fail to reach the market [1]. Problems regarding lack of efficacy and concerns about safety are of paramount importance. Since the removal of a compound due to toxicity may take place at a late stage in drug development, failure costs can be very high. It has been estimated that it costs in the region of \$1400 million, spent over 10 years on average, to bring a new drug to the market [2]. It is, therefore, crucial that compounds that ultimately will be unsuccessful fail at the earliest stage possible, in order to save long-term costs, free up development resources for more promising compounds and avoid adverse side effects in patients.

The hurdles for a new compound to become a registered drug are already very high. As a result,

new drugs can generally be regarded safe and effective in treating the condition for which they were developed. More and more drugs, however, are introduced to target either chronic diseases like diabetes and Alzheimer's or widespread conditions like obesity. Long-term therapy and the sheer number of patients being treated both potentially increase the risk that rare but serious side effects, which are unlikely to be observed during drug development, may become apparent only after market introduction [3]. At the same time, Society has become less prepared to accept therapy-related risks. As a consequence, it is proving increasingly difficult to weigh the benefits of a drug designed to benefit the vast majority of patients against the possible risk of serious adverse effects for a small minority. The lack of knowledge about the exact (molecular) mechanism of action of many drugs and the mechanism underlying potential side effects only compounds this problem.

It has become clear that discrete genetic alterations between individuals can result in significantly different efficacy and safety properties of drugs [4]. Typically, this is due to differences in the affinity of a drug for off-target receptors or alternative metabolic modification of the drug or underlying, unrecognized enzyme deficiencies, resulting in increased susceptibility of individual patients. Effects like these may have been the cause of the low frequency of adverse events that led to the withdrawal of products like Merck's Vioxx and Bayer's Lipobay (Baycol in the US) [5,6]. Therefore, the challenge for pharma is to improve the prediction of rare safety risks and increase the understanding of on-target and off-target modes of action of drug candidates. Large-scale application of the new, molecular assays (i.e. 'omics' technologies) is seen as the big hope to drive this generation of additional knowledge.

The focus of this article is on describing the current trends concerning the application of omic approaches in drug safety assessment, with

specific emphasis on the role of public–private partnerships in advancing this emerging area.

### Current challenges in preclinical toxicology

The aim of preclinical toxicology is to determine the potential risk a compound poses to man, based on the use of surrogate *in vitro* and *in vivo* models [7]. Toxicology is a well-established, scientific domain. Conventional methods in toxicology testing are already fully developed and leave little room for optimization. Efforts to develop new models, for example, based on cell culture or specifically engineered animals, are underway but have not provided any major breakthroughs as yet. Traditionally, toxicology departments are regarded as ‘compound killers’. More recently, the tremendous cost of discovering toxicity late in the development process has triggered a change of attitude amongst drug discovery scientists and management. Previously, toxicology testing would take place just before and in parallel to moving a compound into the first clinical phase. The long-term studies (e.g. examining reproductive toxicity, carcinogenic potential and extended exposure), overlap with clinical development. Companies now try to assess the toxicity of new compounds much earlier in order to manage their pipelines more efficiently and prevent late stage attrition.

Toxicological studies commonly involve the use of multiple animal species, tissue and bacterial cultures, and other test systems. Therefore, the question of relevance of the test system is highly important, that is, will a compound that appears safe *in vitro* or in animals be safe for humans? Problems can arise, for example, from differences in absorption, distribution, metabolism, and elimination (ADME) capacities between species, leading to contradictory results. The ability to predict toxicity in human patients from studies in animals or *in vitro* models, whilst satisfactory for some target tissues, is unsatisfactorily low for others, for example, particular liver toxicities. A survey by the International Life Science Institute (ILSI) revealed a surprisingly large rate of false negatives for some types of toxicity [8]. False positive rates (compounds dropped for apparent toxicity in non-clinical assays but actually non-toxic in human patients) obviously can only be guessed, as knowingly exposing humans to apparent toxins is ethically unacceptable. The choice of the right animal model or other test system is one of the most active areas of dispute between toxicologists. As a default, both a rodent and a non-rodent model are used in the hope that at least one of these will be relevant to man. Finally, the costs associated with a full toxicological assessment can be burdensome and time-consuming.

### Advent of omic technologies in drug safety assessment

Omic technologies are now pervasive within all aspects of the drug development cycle and particularly in the non-clinical phase (Figure 1). The various subdisciplines include transcriptomics (mRNA), proteomics (proteins) and metabolomics (metabolites), amongst a host of other emerging areas [9–12]. Transcriptomic (or toxicogenomic) profiling via the use of DNA microarray-based approaches has arguably provided the most striking advances with respect to our understanding of both disease mechanisms and the effects of drug treatments [10,11]. Omic profiling strategies in drug safety assessment can be divided into two principal domains, namely (1) mechanistic studies to learn more about the mode of action (MOA) of certain toxic compounds; this is important as specific mechanisms carry more weight than others in terms of human toxicity and (2) predictive studies that seek markers for the prediction of whether a certain compound will be toxic to humans or not.

Any change in the established toxicological practice must be justified by clear benefits, for example, saving costs, or reducing the error rates of the evaluations. To prove their maturity, there is a requirement to show that newer strategies generate at least the same quality of results as

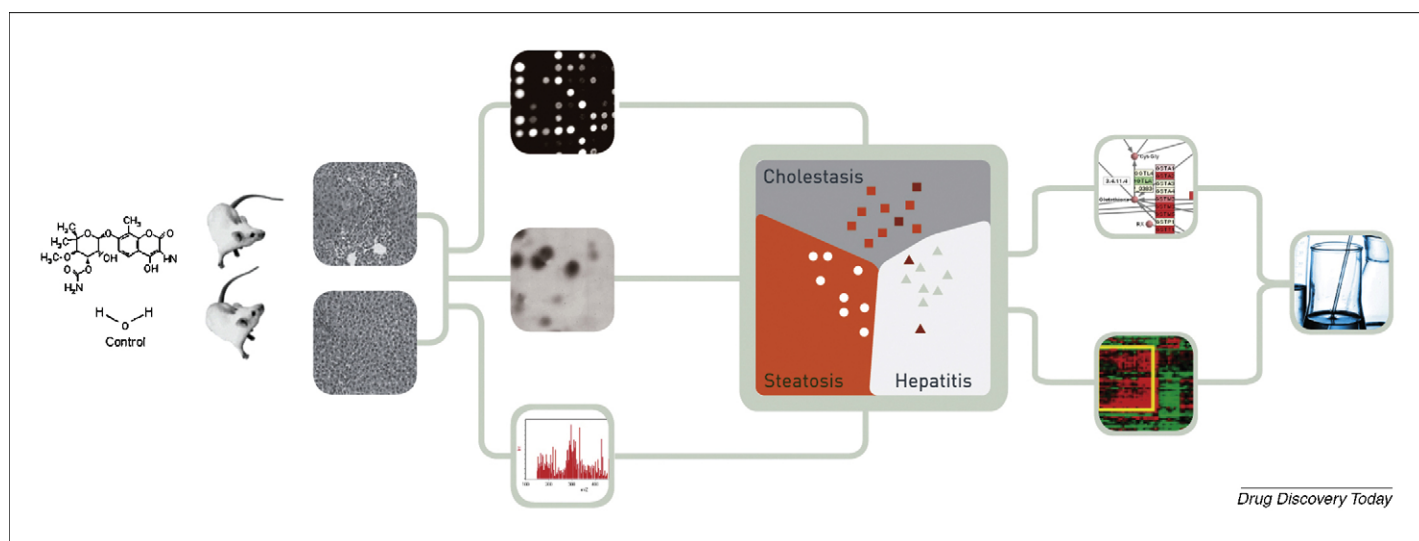


FIGURE 1

Typical omics-based workflow in non-clinical drug development. The initial steps are identical to conventional toxicology studies: animals are treated with a compound under controlled conditions. The study schedule may involve one or several applications of the compound and various blood and urine sampling steps before treated and control animals are finally sacrificed and undergo necropsy including full pathological assessment. During the omics assessment phase, predefined tissue samples (e.g. liver, kidney, blood) from the animals are subjected to either or all of transcriptomics, proteomics and metabolomics assays. In the subsequent bioinformatics phase, the resulting data are processed and analyzed either separately for the different data types or, in an integrated fashion, to give rise to models describing the mode of action (MOA) and/or mode of toxicity (MOT) of a particular compound or sets of markers that can be used to predict the toxic potential of further compounds. In any case, the results of the analysis have to be validated during follow-up studies before they can be applied productively.

the traditional methods. The chances are considered to be highest for early prediction of outcomes, that is, competing with the long-term standard protocols for carcinogenicity [13–16] and reproductive toxicity. There is also a hope of improving the sensitivity of prediction, particularly in areas like hepatotoxicity for which current methods often show unsatisfactory concordance between preclinical and clinical findings [17].

### Application of omic data in decision making: outstanding issues and next steps

Some of the unsolved questions about the productive application of omic profiling approaches for drug safety evaluation and their acceptance by regulatory authorities are due to the relative novelty and the rapid development of this burgeoning field. The following issues will need to be addressed before such technologies are to be widely accepted:

- Standardization of protocols for studies and assays
- Comparability and reproducibility of assays
- Consensus on the data analysis strategy, and the meaning and validation of the markers

For the foreseeable future, both traditional and emerging approaches to toxicological assessment will continue to be applied. In order to define meaningful categories within reference compendia (for prediction) and also to enable biological understanding of the molecular findings, it will be vitally important for researchers to integrate as much of the available information on alternative readouts (e.g. blood chemistry, histopathology) and jointly analyze the data. This

means that, as a first step, data need to be brought together, ideally in a joint database that would support integrated data analysis. Additionally, it is still unclear which molecular level measurements generate the best results for toxicity characterization or prediction. Probably, the most robust set of markers will be composed of a combination of different omic and traditional endpoints.

### Role of public–private partnerships

Creating large reference data collections of toxicology-oriented omic data and comparing these to new experiments and compounds entails huge cost. In addition, the scale of animal testing required to create these compendia independently at each pharma company is ethically problematic. The market is currently exploring two principal ways to circumvent these issues: outsourcing to specialized companies and the formation of consortia. In respect to outsourcing, omic profiling has not been successfully established thus far in the drug safety arena. A major reason for this seems to be that the early adopter service companies were focusing on generating content too early and had difficulty leveraging this investment when the technological development moved on. On the other hand, several consortia have emerged in recent years, often centred on public–private partnership models, whereby industrial, academic and other not-for-profit groups have collaborated together to demonstrate the viability of various omic-based platforms (Table 1). Building productive reference databases is ranked as a mid-term to long-term goal in most

of these initiatives, along with determination of standard practice for assays and analysis [18]. Crucially, these consortia provide a melting pot of ideas, expertise and a means to consolidate resources in technologically demanding areas.

### Chemical Effects in Biological Systems (CEBS)

Funded by the US NIEHS, the objective of CEBS is to integrate omic data with traditional toxicology/pathology endpoints, for the early prediction of key toxicities [19]. The database currently contains information from 27 studies, predominantly from rats or mice dosed with selected compounds. Currently, most of the test compounds are not pharmaceuticals, but industrial chemicals. To date, omic data within CEBS have been mostly restricted to the transcriptomic arena only, albeit there has been some effort in relation to proteomic analysis. CEBS is continuously funded and, since 2008, has been moving forward into a new development phase; apparently, the database design will be revisited, in order to represent additional data types better. In addition, it is foreseen that CEBS shall host the data of complementary public projects like the MicroArray Quality Control (MAQC) project (in particular, the second phase) and some of the datasets from the Health and Environmental Sciences Institute (HESI) toxicogenomics projects, as well as short-term testing results obtained by the US NTP Interagency centre for the Evaluation of Alternative Toxicological Methods (NICEATM). In addition, it is envisaged that data from high-throughput screening studies will be added to the CEBS database.

TABLE 1

#### Public–private partnerships using omics approaches in drug safety assessment

Consortium title	Website	Technologies represented <sup>a</sup>	Species and study design
CEBS programme of the US NIEHS	<a href="http://cebs.niehs.nih.gov/">http://cebs.niehs.nih.gov/</a>	Transcriptomics, proteomics	Rat/mouse; primary focus on liver
Japanese toxicogenomics project	<a href="http://www.tgp.nibio.go.jp/index-e.html">http://www.tgp.nibio.go.jp/index-e.html</a>	Transcriptomics	Rat plus <i>in vitro</i> ; primary focus on liver
FDA and BG medicine liver toxicity biomarker study	<a href="http://www.fda.gov/CDER/livertox/presentations2006/mcburney.htm">http://www.fda.gov/CDER/livertox/presentations2006/mcburney.htm</a>	Transcriptomics, proteomics and metabolomics	Rat; focus on liver
C-path institute: Predictive Safety Testing Consortium—PSTC	<a href="http://www.c-path.org">http://www.c-path.org</a>	Clinical pathology markers	Rat and human markers being sought for liver, kidney, myopathy, vasculitis and carcinogenicity
COMET project	<a href="http://www.metabolomics.net/index.aspx?ID=64360">http://www.metabolomics.net/index.aspx?ID=64360</a>	Metabolomics	Rat; analysis of urinary markers for toxicity (liver and kidney toxins)
HESI Genomics Committee	<a href="http://www.hesiglobal.org/">http://www.hesiglobal.org/</a>	Transcriptomics	Multiple projects, mostly using the rat and <i>in vitro</i> ; markers for kidney, heart and genotoxicity being sought
InnoMed PredTox	<a href="http://www.innomed-predtox.com">http://www.innomed-predtox.com</a>	Transcriptomics, proteomics and metabolomics	Rat (focus on liver and kidney tissues, plus blood/urine)

<sup>a</sup> To date.

### Japanese Toxicogenomics Project

Overseen by the Japanese NIHS and NI Biomedical Innovation Institute, the Japanese Toxicogenomics Project involves 16 Japanese pharmaceutical companies. The first phase of the project began in 2002, with experimental work being completed in 2007. The project aimed to examine the toxicological effect of 150 test compounds (of mainly medicinal interest) in the rat at different timepoints following single and repeat doses, with a focus on transcriptomic assessment of liver and kidney. *In vitro* studies using rat and human hepatocytes were planned to facilitate cross-species bridging. This project has yielded some new insights into mechanism of action and data analysis strategies [20,21], although there have been some problems, such as the small number of replicates, choice of vehicle (e.g. corn oil has been found to alter expression of genes controlling lipid metabolism) and switch of microarray platform midway during the project. The second phase of this project was launched in April 2007, with a five-year timeframe. The particular focus of this newer project is on developing suitable analysis approaches and exploring toxicity biomarkers, with assessment of peripheral blood cells included. Data from a further 30 compounds will be added.

### FDA and BG Medicine Liver Toxicity Biomarker Study

This project was launched in 2005 as a response to the FDA Critical Path Opportunities document. Following the initial agreement between BG (Beyond Genomics) Medicine and the FDA, pharmaceutical companies were invited to join. The focus here was on compounds that were silent in preclinical testing, but had overt hepatic effects in the clinic. Five compound pairs (each pair having similar structure and therapeutic mechanism) were to be studied in a conventional 28-day rat study; in this case, one member of each pair possessed toxicity in the clinic, whilst the other member was denoted as 'clean' or not mediating any toxicity. In terms of technological platforms being used, this effort is employing transcriptomics, proteomics, metabolomics of samples from liver and body fluids. The approach used in the analysis of omic data has been published [22].

### C-Path: Predictive Safety Testing Consortium (PSTC)

The Critical Path Institute (C-Path) is a non-profit, publicly funded organization that serves as a 'neutral ground' for scientists from the FDA/EMA, academia and the pharmaceutical industry to collaborate for the betterment of

public health. The goals of the Predictive Safety Testing Consortium (PSTC) are (a) to validate predictive animal model-based biomarkers aimed at reducing the cost and time involved in conducting non-clinical safety studies, (b) to provide potential early indicators of clinical safety in drug development and post-marketing surveillance, and (c) to provide new tools to assist in regulatory decision-making (see: [www.c-path.org/PredictiveSafetyTestingConsortium/tabid/219/Default.aspx](http://www.c-path.org/PredictiveSafetyTestingConsortium/tabid/219/Default.aspx)). A key area of attention is that the PSTC is centred on the qualification of candidate biomarkers. The main approach used is for member companies to share data, samples and assays in efforts to cross-validate panels of markers. Current foci are on biomarkers of hepatotoxicity, nephrotoxicity, vasculitis, myopathy as well as genotoxic and non-genotoxic carcinogens [13]. Particularly noteworthy was the first submission of its kind, by the PSTC Nephrotoxicity Working Group, to the FDA under its Voluntary Exploratory Data Submission (VXDS) process, in respect to data from 23 compounds for seven biomarkers. The target toxicities in respect to this submission related to proximal tubular damage and glomerular damage/alterations (see: <http://www.fda.gov/bbs/topics/NEWS/2008/NEW01850.html>).

### Consortium on Metabonomic Toxicology (COMET)

Led by a research group at Imperial College London, the first phase of the COMET project was attempting to validate the use of metabolic profiling data in the prediction of drug toxicity, with emphasis on liver and kidney toxins. In this case, urinary metabolites were measured using <sup>1</sup>H-NMR, with >80 treatments (including >20 drugs) having been studied, covering a wide range of chemical structures. So far, COMET has provided key insights into intersite reproducibility, along with information on analytical and biological variation with respect to measurements taken [23]. Moreover, this project has managed to detect relevant metabolic profiling signatures that characterize various treatments, allowing the identification of target organs at subtoxic levels [24].

### Health and Environmental Sciences Institute (HESI) Genomics Committee

This grouping has four related projects at present, namely (1) a state-of-the-science survey to examine multi-sector perceptions and experience in the application of toxigenomics to safety evaluation, (2) to establish a baseline animal database, comprising voluntarily contributed transcriptomic data from rats in the untreated

context, (3) to establish mechanism-based markers of toxicity, with an initial focus on a collaboratively designed rodent cardiotoxicity study and (4) to examine utility of transcriptomic approaches to assessing genotoxic potential. Most of these projects are in progress with publications expected in the near future.

### InnoMed PredTox as a case study

The InnoMed PredTox consortium, which is coordinated by the European Federation of Pharmaceutical Industries and Associations (EFPIA), was established in October 2005 via joint funding from the European Commission under Framework Programme 6 and in-kind contributions from participating companies. This consortium, which involves 14 pharmaceutical, three academic institutions, and two technology providers, is centred on benchmarking the utility of integrating a multi-omic approach (transcriptomics, proteomics and metabolomics), together with conventional histopathological and clinical chemistry data, for better insights into non-clinical safety. The focus of the InnoMed PredTox project has been on characterizing the hepatotoxic and/or nephrotoxic effects of 14 proprietary compounds which have failed during the non-clinical development phase, contributed by the various member companies, along with two reference compounds (troglitazone and gentamycin). Crucially, the study design is the same for all compounds selected (Figure 2), which paves the way for integration of these complex and diverse data types, with a dedicated relational database having been constructed by Genedata (see: [www.genedata.com](http://www.genedata.com)). In addition, a comprehensive repository of digital images (>1700) of kidney and liver histopathological specimens was created and linked to the central database through an online interface [25]. The design of the InnoMed PredTox project is unique with respect to the number of assay technologies used to assess toxicity of the compounds, as well as the level of integration of data and analyses across the technologies and individual studies. During the project, this approach has been used to gain additional mechanistic understanding of toxic effects and suggesting new biomarkers [26,27]. Expert working groups were established focusing on specific pathological effects common to several studies, namely liver hypertrophy, bile duct damage/hepatocyte necrosis and general nephrotoxicity. The project has identified several potential biomarkers that are being studied in more detail by the academic partners within the consortium. This has allowed confirmation of the specificity of some markers and

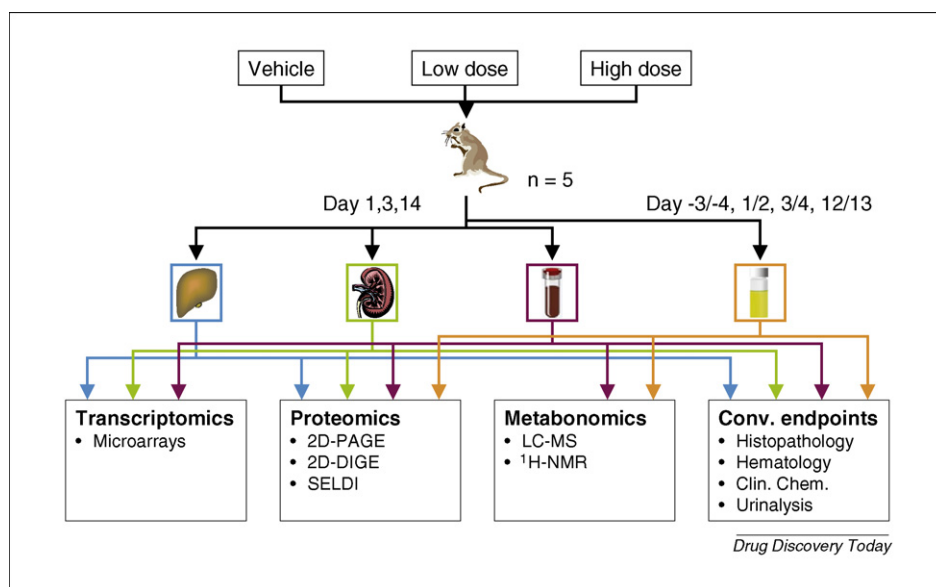


FIGURE 2

Experimental design overview of the InnoMed PredTox project. Sixteen compounds with known hepatotoxicity and/or nephrotoxicity were used to treat groups of male Wistar rats ( $n = 5$ ) at three dose levels (vehicle alone, low dose, high dose) and with target tissue (liver and kidney) and biological fluid samples (blood, urine) taken at several evaluation time points (24 h, three days and 14 days). Investigations performed on these materials included the use of classical assessment approaches (histopathology, clinical chemistry) and three omics approaches, namely transcriptomics (Affymetrix GeneChips), proteomics (2D-DIGE, 2D-PAGE, and SELDI) and metabolomics (LC/MS and NMR).

has shown that other markers are more general markers of tissue damage or inflammation. This approach has been particularly successful in studying kidney markers of damage.

One of the principal objectives of this study was to determine whether the integration of 'omic' technologies with conventional histopathology and clinical chemistry can allow decision-making to progress or terminate a drug candidate earlier than would be achieved by reliance on conventional techniques alone. This pilot study has given some indication that this may be possible, with some gene signatures and potential new biomarkers showing compound-related changes at lower doses and earlier timepoints than frank histopathological changes. The successful collaboration of large pharma, small to mid-size enterprises and academia within InnoMed PredTox finds its expression in the proposal of a comparable project under the umbrella of the newly formed Innovative Medicines Initiative [28]. Several publications summarizing the results of the project are currently in preparation.

## Conclusions

Omic profiling has an important role to play in the present and future of mechanistic understanding of toxicity. Evidence is steadily accumulating that these technologies can help decision-making earlier than is possible with traditional techniques, but it is also clear that, at

present, traditional methods, such as histopathological assessment, still occupy a central position in safety assessment. Integration of all these technologies provides a powerful approach to understanding the toxicological process and, with this, will result in better and more informed decision-making during compound development. Omic technologies require substantial resource commitments. This provides a challenge to individual companies in taking this approach forward. Public-private partnerships are one solution to this problem, with this article showing how such approaches can be very productive. The InnoMed PredTox as a specific example has demonstrated the feasibility of this approach on the basis of close interdisciplinary collaboration of scientists as well as a suitable database and analysis infrastructure. Nevertheless, we are still quite away from making full use of an integrated assessment, which needs further projects of this type. It can be expected that the quality of prediction will increase with the size and the level of associated information of reference compendia of tested compounds from a variety of toxic compounds, acting via different mechanisms and including studies in the different species used in toxicology. This in turn leads to the need for growing and maintaining these databases over a considerable timeframe. For these comprehensive data collection, annotation and documentation efforts, thorough compliance to

standard operating procedures and sustainable storage of the data are absolutely essential. Training of biologists in systems toxicology is also essential to allow interpretation of these complex datasets. This wave of knowledge will also provide challenges for regulatory authorities and it is essential for progress in this area that these bodies keep abreast of this approach and continue to contribute to future projects.

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## References

- 1 European Federation of Pharmaceutical Industries and Associations, (2008) *The Pharmaceutical Industry in Figures* ((2008 edn)), EFPIA
- 2 DiMasi, J.A. and Grabowski, H.G. (2007) The cost of biopharmaceutical R&D: is biotech different? *Manage. Decis. Econ.* 28, 469–479
- 3 Schmid, E.F. *et al.* (2007) Communicating the risks and benefits of medicines. *Drug Discov. Today* 12, 355–365
- 4 Eichelbaum, M. *et al.* (2006) Pharmacogenomics and individualised drug therapy. *Ann. Rev. Med.* 57, 119–137
- 5 Daby-Bondoc, S. and Franco, S. (2008) Risk-benefit perspectives in Cox-2 blockade. *Curr. Drug Saf.* 3, 14–23
- 6 Arora, R. *et al.* (2006) Statin-induced myopathy; the two faces of Janus. *J. Cardiovasc. Pharmacol. Ther.* 11, 105–112
- 7 Tweats, D.J. (2005) Preclinical Safety Testing. In *The Textbook of Pharmaceutical Medicine* (5th edn) (Griffin,

- J.P. and O'Grady, J., eds), pp. 111–143, The Queens University of Belfast
- 8 Olson, H. *et al.* (2000) Concordance of the toxicity of pharmaceuticals in humans and in animals. *Regul. Toxicol. Pharmacol.* 32, 56–67
- 9 Borlak, J., ed. (2005) *Handbook of Toxicogenomics: Strategies and Applications*, Wiley-VCH
- 10 Foster, W.R. *et al.* (2007) A retrospective analysis of toxicogenomics in the safety assessment of drug candidates. *Toxicol. Pathol.* 35, 621–635
- 11 Schnackenberg, L.K. and Beger, R.D. (2006) Monitoring the health to disease continuum with global metabolic profiling and systems biology. *Pharmacogenomics* 7, 1077–1086
- 12 Collins, B.C. *et al.* (2007) Use of proteomics for the discovery of early markers of drug toxicity. *Expert Opin. Drug Metab. Toxicol.* 3, 689–704
- 13 Fielden, M.R. *et al.* (2008) Interlaboratory evaluation of genomic signatures for predicting carcinogenicity in the rat. *Toxicol. Sci.* 103, 28–34
- 14 Vinken, M. *et al.* (2008) The carcinoGENOMICS project: critical selection of model compounds for the development of omics-based *in vitro* carcinogenicity screening assays. *Mutat. Res.* 659, 202–210
- 15 Ellinger-Ziegelbauer, H. *et al.* (2009) Application of toxicogenomics to study mechanisms of genotoxicity and carcinogenicity. *Toxicol. Lett.* 186, 36–44
- 16 Ellinger-Ziegelbauer, *et al.* (2008) Prediction of a carcinogenic potential of rat hepatocarcinogens using toxicogenomics analysis of short-term *in vivo* studies. *Mutat. Res.* 637, 23–39
- 17 Uetrecht, J. (2008) Ideosyncratic drug reactions, past, present and future. *Chem. Res. Toxicol.* 21, 84–92
- 18 Mattes, W.B. (2008) Public consortium efforts in toxicogenomics. *Methods Mol. Biol.* 460, 221–238
- 19 Waters, M. *et al.* (2008) CEBS—Chemical Effects in Biological Systems: a public data repository integrating study design and toxicity data with microarray and proteomics data. *Nucleic Acids Res.* 36, D892–900
- 20 Kiyosawa, N. *et al.* (2006) Utilization of a one dimensional score for surveying chemical-induced changes in expression levels of multiple biomarker gene sets using a large scale toxicogenomics database. *J. Toxicol. Sci.* 31, 433–447
- 21 Uehara, T. *et al.* (2008) Species specific differences in coumarin-induced hepatotoxicity as an example of toxicogenomics-based approach to assessing risk of toxicity to humans. *Human Exp. Toxicol.* 27, 23–35
- 22 Adourian, A. *et al.* (2008) Correlation network analysis for data integration and biomarker selection. *Mol. Biosys.* 4, 249–259
- 23 Lindon, J.C. *et al.* (2005) The Consortium for Metabonomic Toxicology (COMET), aims, activities and achievements. *Pharmacogenomics* 6, 691–699
- 24 Nicholson, J. (2007) COMET and the challenge of drug safety screening. *J. Proteome Res.* 6, 4098–4099
- 25 Mulrane, L. *et al.* (2008) Creation of a digital slide and tissue microarray resource from a multi-institutional predictive toxicology study in the rat: an initial report from the PredTox group. *Exp. Toxicol. Pathol.* 60, 235–245
- 26 Mally, A. (2008) Omics in hepatotoxicity prediction. *The Toxicologist CD 102*, Number S-1, Abstract ID 1269
- 27 Staedtler F. (2008) An integrated-omics approach towards a better understanding of drug-induced nephrotoxicity and useful biomarkers. *The Toxicologist CD 102*, Number S-1, Abstract ID 1270
- 28 Hunter, A.J. (2008) The innovative medicines initiative: a pre-competitive initiative to enhance the biomedical science base of Europe to expedite the development of new medicines for patients. *Drug Discovery Today* 13, 371–373

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