

Handbook of Toxicogenomics

Strategies and Applications

Edited by
Jürgen Borlak



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To the memory of my parents

Forewords

Genome research, combinatorial chemistry and high throughput screening methods yield a large number of target structures and potential pharmaceutical agents. Numerous substance candidates in the pharmaceutical industry, however, are doomed to fail during the preclinical or even clinical development phase because their toxicity is not recognized in time. Fast and economic tox screening tests which are nevertheless meaningful for humans are, therefore, urgently required, so that the substances with the most promising potential can be prioritized. Such prioritization should be accomplished as soon as possible, i. e. before entering into the costly development phase.

The German Federal State of Lower Saxony, therefore, supports the initiative of the Fraunhofer Institute of Toxicology and Experimental Medicine (ITEM) to considerably enhance its focus on Pharmaco- and Toxicogenomics, which has been successfully operated for several years by now and has recently become a center of excellence. A genome-based understanding of drug and chemical toxicity is of paramount importance and required as to develop meaningful methods for predictive toxicity testing. One core technology is based on microarrays but methods to study the proteom are essential as well. These genomic platform technologies are highly costly. The Federal State of Lower Saxony supports and fosters the development of competence clusters, spin-offs as to enable the pharmaceutical industry to equally make use of these technologies. The German Federal State of Lower Saxony has therefore provided substantial funding to enable the Fraunhofer Institute of Toxicology and Experimental Medicine to develop novel methods for predictive toxicology and to become internationally competitive in chemical and drug safety testing. Therefore, Pharmaco- and Toxicogenomic research at the Fraunhofer Institute in Hanover has become a hallmark for the capital city of Lower Saxony. Further, the German Federal Government program “Gesundheitsforschung – Forschung für den Menschen”, an initiative to promote research for human health, places the emphasis on an integration of basic and applied research and on the exploitation of the results by the industry. This is way the Fraunhofer Institute of Toxicology and Experimental Medicine in Hanover is perfectly suited to fulfill this task.

Lutz Stratmann

Minister for Science and Culture, Lower Saxony

With the advent of sequence information for the entire genome of many species, it is now possible to analyse gene expression and genetic variability on a global scale. It is therefore feasible to study gene expression profiles in entire genomes and to use this information for a mechanism based risk assessment. In conjunction with an assessment of entire proteomes it is now possible to develop early diagnostics and preventive measure particularly in at-risk populations or individuals. The Fraunhofer Institute of Toxicology and Experimental Medicine is well suited to carry out basic and applied science as to foster an understanding of chemical and drug induced toxicity. Indeed, in depth collaboration between academia and industry is of major importance to reduce attrition rates in the search for and development of new drugs and the Fraunhofer-Gesellschaft with its institutes has been practicing this principle with much success for several decades already. The creation of vast amounts of genomics and toxicogenomics data has sparked the development of novel systems as to improve predictability of drug response at toxic dose levels and the Food and Drug Administration (FDA) has recently issued a draft “Guidance for Industry” Pharmacogenomics Data Submission (FDA 2003) to account for these developments in medical sciences. Specifically, many principles in this draft apply to toxicogenomics and the newly created tool for voluntary submission of genomics data will pave the way in advancing public health and drug development based on holistic information. The Fraunhofer Institute of Toxicology and Experimental Medicine is committed to provide leadership in this field of genomic science and to develop mechanism based understanding of toxicity for an improved risk assessment of human health.

Hans-Jörg Bullinger

President of the Fraunhofer-Gesellschaft

The pharmaceutical industry is continuously facing increasing costs for developing new drugs on one hand and a high incidence of pipeline dropouts due to unexpected toxicity on the other hand. Furthermore, rare but serious adverse drug reactions still occur when new drugs are being used without being detected during development by preclinical or clinical studies. Therefore, new technologies that can predict more precisely the liabilities of drugs in early and late development are considered highly valuable. There are currently various new technologies under evaluation or even already in routine use to improve the prediction of drug-related side effects. One of these technologies is toxicogenomics, a concept which is intensively described and explained in the new “Handbook of Toxicogenomics” edited by Prof. Dr. Jürgen Borlak. This handbook provides an impressive overview of the current knowledge on the various technological platforms in the field of toxicogenomics. The topic of bioinformatics, which plays a key role in this field, is also addressed in detail. In addition, various authors from both academia and industry provide the reader with an overview of the current practical applications of toxicogenomics in fields such as hepatotoxicity, nephrotoxicity and search for biomarkers. The “Handbook of Toxicogenomics” is therefore considered to provide a comprehensive insight into the basic concepts of a new technology with the potential to positively impact human safety assessment in the near future.

Andreas Barner

Chairman of the Verband der Forschenden Arzneimittelhersteller, e.V.

Research and development in the fields of toxicology and pharmacology are currently undergoing drastic changes. New findings in the areas of molecular pharmacology/toxicology, molecular genetics, functional genomics, molecular immunology and cell biology open up new possibilities in the search for and development of pharmaceutical agents. In this context, the interdisciplinary development of pharmaceuticals has become particularly important, and the integration of the areas of genomics, molecular biology, surface technology, optics, robotics and combinatorial synthesis plays an important part in the creation of miniaturized and automated screening methods. The development of HTS (high throughput) systems, for instance, allows for millions of drug substance candidates to be evaluated within a single year in an almost completely automated laboratory. A toxicological assessment of drug substance candidates at an early stage is, however, a mandatory condition for the HTS strategy to be successful. Therefore a close interplay between academic and industrial research is of pivotal importance since for the pharmaceutical companies it is becoming increasingly impossible to cover the whole range of technologies and competences by themselves. Further, the high attrition rate in the R&D process and post launching drug failures due to adverse drug reactions requires an in-depth understanding of the mechanism of toxicity.

The Fraunhofer Institute of Toxicology and Experimental Medicine with more than 20 year experience of drug and chemical safety testing has now become a center for Pharmaco- and Toxicogenomic Research as well and the center has developed an international network of strong collaboration with academic and industrial collaborators including the National Institute of Health in the US and Japan. Undoubtedly, toxicogenomics is on the path to evolve into an independent genomic science as to enable prediction of toxicity based on a systems biology approach.

Uwe Heinrich

Chairman of the Fraunhofer Life Sciences Alliance

Preface

Toxicogenomics is a rapidly growing field of genomic science and holds promise for the identification and development of new founded knowledge in human and animal health. Basically, all major genomic platform technologies are being applied to toxicogenomic research and this includes transcriptome and proteome analysis as well as hyphenated LC-MS-NMR technology used to obtain metabolic fingerprints during intoxication and disease. Therefore, this book captures expert knowledge and provides in depth information on an application of toxicogenomics for the prediction of adverse drug reaction and for an improved understanding of the molecular basis of drug induced toxicity. There is also vision of how toxicogenomics will develop in the future and for communicating the challenges for it's application in risk assessment and to obtain regulatory acceptance. The book is divided into four major sections and starts with in-depth information on the various genomic platforms applied to toxicogenomic research. This is followed by a thorough discussion on bioinformatic tools, novel genetic algorithms and the architecture of various databases. It includes a description of the the Chemical Effects and Biological Safety database of the National Institute of Environmental Health Sciences (NIEHS of the US) and an appreciation of the various software applications used to analyse toxicogenomic data. Because of it's considerable importance a systems biology approach to toxicogenomics is described as well. In the third section the reader will be informed on fine examples of toxicogenomic research and this includes, amongst others, the prediction of hepato-, cardiovascular-, nephro- and haematotoxicity as well as endocrine disruption. One contribution focuses specifically on the application of toxicogenomics to teratogenicity studies and therefore this section highlights successful applications of toxicogenomics to predict drug induced toxicity. The fourth section gives an account of various national toxicogenomic programs and a perspective of an ICH harmonised guideline for inclusion of toxicogenomic data into the drug registration process.

In conclusion, the vast amounts of genomics and toxicogenomics data has provided novel insight into the molecular basis of drug induced toxicity. Inevitably, this knowledge will impact chemical- and drug safety testing and has initiated a fundamental shift of paradigm with the consequence of developing novel and above all better approaches for the prediction of drug induced toxicity.

I very much hope this book will become a stimulating resource for investigative toxicology with the aim to continuously improve strategies for predictions of unwanted drug effects and drug induced toxicities.

Jürgen Borlak

Hanover, January 2005

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