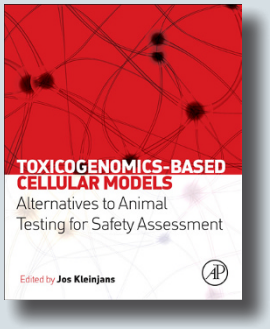
Evaluating toxicity mechanisms using DNA

Reviewed by Roshan Kumar Sahu, M. Pharm. & Kamal Kishor



TOXICOGENOMICS-BASED CELLULAR MODELS: ALTERNATIVES TO ANIMAL TESTING FOR SAFETY ASSESSMENT

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Drug toxicity must be evaluated throughout the drug discovery and development processes, both during *in vitro* and *in vivo* preclinical testing and during clinical trials. There have been several advances in the field of toxicology and improvements in toxicity evaluation methods. After cell-based models were introduced, it became easier to assess the toxicity of drugs without the use of animals as well as to evaluate cell-specific toxicity. Animal- and cell-based models have a few drawbacks, however. For example, they cannot be used to determine the molecular mechanisms of toxicity.

DNA microarray technology has several advantages over existing toxicity assessment systems. Using microarrays, pharmacologically active genes and genes involved in toxicity can be monitored simultaneously. The technology has also ushered in the concepts of genomics, pharmacogenomics and bioinformatics, which together have provided the foundation for the field of toxicogenomics[1,2]. The study of gene and protein responses to toxic substances has made predictive toxicology possible and toxicological assessment of chemical substances easier, faster and more efficient.

These ideas are explored in detail in a book titled *Toxicogenomics-Based Cellular Models: Alternatives to Animal Testing for Safety Assessment*. The book describes the development of state-of-the-art cellular models and provides a compilation of new methods and assays to assess the toxicity of drugs and other chemical substances. The first section of the text introduces the use of cell-based models in toxicology research and describes how existing models may be adapted for toxicogenomic studies.

Section 2 of the book focuses on genotoxicity and carcinogenesis, discussing these topics in both basic and advanced terms. The section describes approaches to determining the mechanisms of these effects and applications of *in vivo* genomics to their prediction. Other subsections pertain to DNA damage, the signaling responses that result and the use of RNA-interference screening to identify these signaling responses.

The third section, on the topic of immunotoxicity, describes in detail the relevant mechanisms and pathways. The shortcomings of existing chemical safety evaluation techniques are contrasted with the strengths of applied toxicogenomic approaches to predicting chemical safety. The section also provides a detailed description of chemical sensitization, with a primary focus on skin sensitization. Although the skin is commonly used as a chemical sensitization model for the toxicogenomic analysis of cutaneous responses, alternative sensitization models that mimic the skin have been developed and validated. The final chapter of this section compares current evaluation methods using human, rodent and alternative models with toxicogenomic and bioinformatic approaches.

The fourth and fifth sections address reproduction toxicity and organ toxicity, respectively. The former primarily focuses on transcriptomics, its implementation in various testing models and new approaches such as *in vitro* developmental toxicity testing. A discussion of thyroid toxicogenomics provides a mechanistic approach for multi-organ toxicity testing. In contrast, Section 5 focuses on toxicogenomic assessment of organ-specific toxicity of the liver or kidney. This section provides novel information about the correlation of organ-specific toxicity with circadian rhythms.

Later sections are dedicated to toxicoinformatics and the selection and validation of testing models for toxicogenomic assays. Databases and other sources of information about toxicogenomics and systems toxicology; data collection, interpretation and analysis methodologies with application to bioinformatics; and strategies for implementing toxicogenomic tools are discussed in detail.

This book is a great example of how interdisciplinary sciences can be applied for the development of enhanced research approaches. The book introduces the conception, selection, validation and implementation of different toxicogenomic strategies. It provides an in-depth reference for those in the field of toxicology and chemical safety assessment. This book is within the scope of not only academics but also basic scientists and clinical, pharmaceutical, cosmetic and drug development researchers.

Sahu is at the Open Source Drug Discovery Unit, Council of Scientific and Industrial Research, New Delhi, India. Kishor is in the Department of Chemistry, Jodhpur National University, Jodhpur, India.

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