According to the Institute of Medicine and the U.S. Food and Drug Administration, “developing new scientific approaches to detecting, understanding, predicting, and preventing adverse events” was a critical path to the future of drug safety. This book brings together a collection of state-of-the-art chapters, written by experts in the drug safety field. It provides information on the present knowledge of drug side effects and their mitigation strategy during drug discovery, gives guidance for risk assessment, and promotes evidence-based toxicology. Each specific area of toxicology relevant for drug discovery is discussed in detail, including theory, experimental approaches, and data interpretation supported by comprehensive up-to-date references. Many chapters provide fascinating case studies, which are of general interest for those who have basic science training and are interested in how chemicals interact with the human body.

Dr. Jinghai J. Xu is currently Director of Knowledge Discovery and Knowledge Management at Merck & Company, Inc. Dr. Xu has won numerous awards, including the Central Research Achievement Award and Pfizer Global Research & Development Award. His most recently published book is *Drug Efficacy, Safety, and Biologics Discovery: Emerging Technologies and Tools* (2009).

Dr. Laszlo Urban is currently Executive Director and Global Head of Preclinical Safety Profiling at Novartis Institutes for Biomedical Research. Dr. Urban has been actively involved in organizations such as the European Neuropeptide Club, the Society for Biomolecular Sciences, and the International Association for the Study of Pain. His most recently published work is *Hit and Lead Profiling: Identification and Optimization of Drug-Like Molecules* (2009).
Predictive Toxicology in Drug Safety

Edited by

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In 2007, the U.S. Food and Drug Administration (FDA) issued a report titled “The Future of Drug Safety – Promoting and Protecting the Health of the Public.” In it, strengthening the science that supports drug safety evaluation was recognized as a critical path to improve drug safety assessment. In particular, “developing and qualifying techniques for predictive toxicology” was identified as one of the major unmet needs in advancing scientific approaches to detect, understand, predict, and prevent adverse events (http://www.fda.gov/).

With the cost of developing an FDA-approved medicine approaching $1 billion and time to develop a drug taking 10 to 15 years, late-stage failures or attritions pose a significant burden on the sustainability of the current pharmaceutical research and development (R&D) model. Because 90% of drug candidates that enter clinical development fail to reach the market, the root cause of rising R&D costs is a continuous investment in failure. By last account, clinical safety represents 20% and preclinical toxicology embodies 13% of failed development efforts. Together, drug safety reasons account for one-third of overall failure. Most of the current tools and models used for toxicology and human safety testing are decades old, including many that are recommended by the FDA. Better models, methodologies, and testing paradigms with demonstrated improvement in drug safety prediction than existing practices are clearly needed. Predictive toxicology, aimed at addressing this challenge using a combined knowledge and insight from all fields of science, is the central topic of this book.

This book is organized into two sections. The first section starts with a “current state” chapter on the predictivity of animal toxicology evaluation for human drug safety. This is followed by individual topics of toxicology, including genetic, cardiac, hepatic, drug–drug interactions, reactive metabolite, immune, neurologic, and developmental toxicology. The second section of the book emphasizes integrated approaches (integrated lead optimization, oncology drugs, mechanism-based toxicity), novel in vivo experimental models (zebrafish, genetically engineered models), emerging technologies (toxicogenomic pathway mining, safety biomarkers), and mathematical modeling approaches (PKPD modeling, biologics modeling). The book ends with a chapter on the safety evaluation of vaccines. Each chapter is authored by subject matter experts in that area. We are
extremely grateful to all the contributing authors for sharing their knowledge and insight. It is our honor to experience their enthusiasm, professionalism, and collaboration from the beginning of this book project.

Even though there is a heavy emphasis on drug discovery and development, the predictive toxicology strategies and approaches described in this book should also be highly relevant and applicable to the fields of chemical, environmental, and other areas of toxicology where rational prediction of human safety risk becomes a fundamental duty for toxicologists. We hope that toxicologists in both practice and training will find this book thought-provoking and highly pertinent to the direction of toxicology in the twenty-first century.

Jinghai J. Xu, Ph.D.
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