

Preface

Each human is genetically distinctive, and responds differently to disease-causing factors as well as to drugs. Mechanisms inside human bodies that control drug responses are complex and multifactorial. Pharmacogenomics arose in response to such recognition of the necessity of personalized medicine, a medicine that deals with the complexity of the human body. The development of pharmacogenomics represents the evolution of biomedicine from treating the general disease itself to treating the malfunction of an individual person, the “root” of diseases. With the change of focus from diseases to humans, pharmacogenomics brings hope for the transformation from disease treatment to disease prevention.

Pharmacogenomics is considered the future of drug therapy. For the drug development industry, pharmacogenomics is useful in identifying drug targets to obtain optimal drug efficacy for certain patient populations. Because of the diversity of patients’ biological backgrounds, the same disease may be caused by genetic variations in different people, who will respond differently to the same drug. Such situations require individualized treatment that avoids adverse drug responses and ensures the best possible results.

However, many challenges need to be resolved before pharmacogenomics can be applied in the clinic. These challenges include the identification of biomarker genes and pathways, the understanding of interactions between genes and drugs, and the correlation of genotypes to disease and drug response phenotypes.

In this book, we approach these challenges from three aspects. We first introduce some important cutting-edge technologies that are useful for the development of systems-based pharmacogenomics to solve the complexity; these technologies include bioinformatics, microarray, and association studies. These technologies can help us with the identification of biomarker genes and pathways and in understanding the associations among genes, drugs, and diseases.

These systems-based approaches use bioinformatics methods for studies in pharmacogenomics and systems biology to manage, organize, and understand the overwhelming information. Integrated methodologies and procedures for applying bioinformatics analysis in pharmacogenomics are presented in this book, as bioinformatics has become indispensable for almost all biopharmaceutical studies today. Pharmacogenomics-related resources, including databases and tools, are collected and provided.

Microarrays and biochips are powerful technologies for high-throughput (HTP) analysis that may enable systematic understanding of genomics and proteomics as well as large drug response data sets. The applications of microarrays in pharmacogenomics, genotyping, and clinical diagnosis, as well as the evolution and development history of the technology, are introduced in this book. Different techniques, platforms, and tests are also discussed.

Association study is a useful method in pharmacogenomics for investigating how individuals with unique genetic variants respond to a drug treatment. Confounding caused by population structure and admixture can contribute to the lack of replication of association study results. Methods for detecting and adjusting confounding are explained, as are their advantages and disadvantages.

The second aspect of this volume includes approaches to studying gene–drug interactions, that is, how drugs act and how they are processed in the human body, including drug absorption, distribution, metabolism, and excretion. Biomarkers and molecules such as ion channels, membrane transporters, receptors, and enzymes are playing increasingly essential roles in drug design and pharmacogenomics studies. These biomarkers provide critical links between drug discovery and diagnostics efforts. Updated introductions and detailed methods about studies in these molecules are provided in this book.

For example, membrane transporters are profoundly involved in drug disposition through transporting substrate drugs between organs and tissues. Investigations of genetic variations, genotyping methods, and substrate identification of membrane transporters are helpful for drug design and development. Different methods for assessing functional significance of transporter polymorphisms *in vitro* and *in vivo* as well as the application of transporter genetics in clinical pharmacology are described. Clinical significance of pharmacogenomics studies in drug-metabolizing enzymes and drug transporters for certain treatments, such as chemotherapy, is discussed in detail.

Studies of G protein-coupled receptors (GPCRs) may provide insight into disease pathways, such as the involvement of the regulator of G protein signaling (RGS) protein polymorphisms in hypertension. Pharmacogenomics of GPCR studies the involvement of genetic variations in structural and functional roles, such as GPCR activation and inactivation, their relationships with diseases, and their potential uses in defining optimized novel drug targets. These investigations can be useful for refining drug discovery as GPCR disorders are associated with a wide variety of human diseases, including retinal diseases, thyroid diseases, obesity, diabetes, asthma, cardiovascular diseases, cancer, and infectious diseases.

The third aspect composes a large part of this book: a focus on how pharmacogenomics can be used in therapeutics of diseases. These diseases include cardiovascular diseases, cancer, neurological diseases, gastrointestinal disorders, autoimmune diseases, and infectious diseases. Comprehensive information for each disease system is discussed, including biomarkers involved in the disease and the associations among genes, drugs, diseases, drug response phenotypes, and the environment.

For example, epigenetics and environmental factors may play important roles in major psychiatric disorders. Detailed methods for studying these factors are given to provide a prototype model system for better diagnosis and management of

mental diseases. Asthma is another disease caused by interactions among multiple causes, including demographic, social, environmental, and genetic factors. The most common biological pathways targeted by asthma therapy and the genetic contributions to varied therapeutic responses are described.

Drug treatment in Alzheimer's disease (AD) accounts for more than 10% of direct costs, while fewer than 20% of AD patients are fair responders to conventional drugs. Pioneering pharmacogenomics studies have shown that the therapeutic response in AD is genotype specific as pharmacogenomics factors account for more than 60% of drug variability in drug disposition. This book provides a comprehensive and detailed discussion of the pharmacogenomics of AD, from functional genomics to therapeutic strategies. The integration of these pharmacogenomics protocols with AD drug discovery and clinical practice can help promote therapeutics optimization and develop cost-effective pharmaceuticals to improve both drug efficacy and safety.

For cardiovascular diseases, methods for choosing candidate genes and single-nucleotide polymorphisms (SNPs) and the association with functional studies are discussed. These mechanistic studies are particularly important when it comes to pharmacogenomics associations. These studies provide significant and clinically relevant insights into the variable drug responses in cardiovascular disease management.

In gastroenterology and hepatology, genetic variations involved in drug metabolism or disease pathophysiology have been found to have an impact on drug responses. Discussions in this book focus on clinical pharmacogenomics of inflammatory bowel disease, *Helicobacter pylori* infections, gastroesophageal reflux disease, irritable bowel syndrome, liver transplantation, and colon cancer.

For rheumatoid arthritis, the pharmacogenomics of three major disease-modifying antirheumatic drugs (methotrexate, azathioprine, and sulfasalazine) and one class of biologic antirheumatic drugs (the tumor necrosis factor antagonists) are discussed in detail.

Cancer pharmacogenomics includes studies on biomarkers such as thiopurine methyltransferase (TPMT) and epidermal growth factor receptor (EGFR). Research methods such as germline and tumor DNA studies, polymorphism selection, and biomarker screening as well as genotyping systems are described.

Using array technology in pharmacogenomics, efficacy and systemic toxicity can be evaluated for the improvement of the design and development of preclinical vaccines. Methods of applying pharmacogenomics in the evaluation of efficacy and adverse events during clinical development of vaccines are also discussed.

By covering topics from individual molecules to systemic diseases, from fundamental concepts to advanced technologies, this book intends to provide a practical, state-of-the-art, and integrative view of the application of pharmacogenomics in drug discovery and development. I would like to thank all of the authors for their contributions to this exciting new field. I also thank the series editor, Dr. John Walker, for his help with the editing.

Qing Yan
PharmTao, Santa Clara
CA, USA