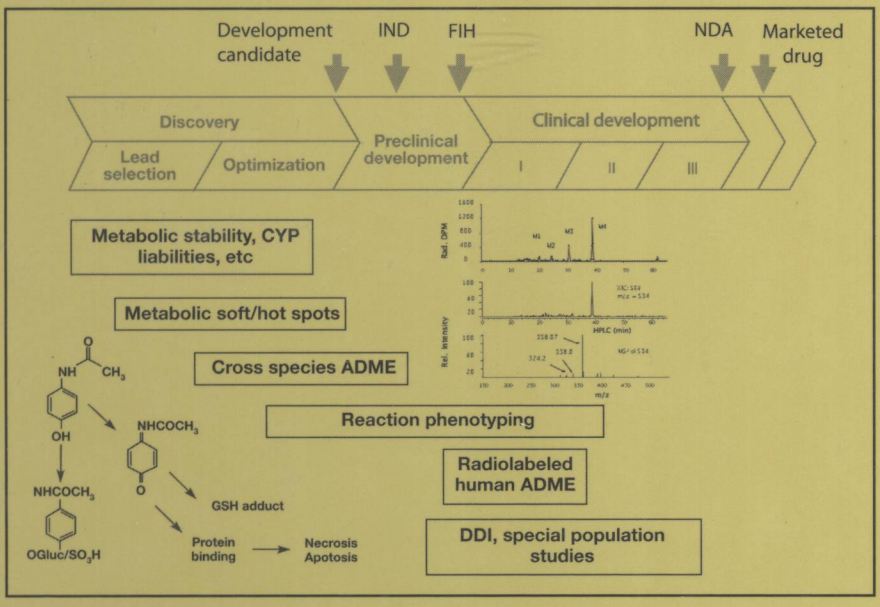
WILEY

DRUG METABOLISM IN DRUG DESIGN AND DEVELOPMENT



Edited by
Donglu Zhang
Mingshe Zhu
W. Griffith Humphreys

DRUG METABOLISM IN DRUG DESIGN AND DEVELOPMENT

Basic Concepts and Practice

EDITED BY

DONGLU ZHANG

MINGSHE ZHU

W. GRIFFITH HUMPHREYS

WILEY-INTERSCIENCE
A JOHN WILEY & SONS, INC., PUBLICATION

Published by John Wiley & Sons, Inc., Hoboken, New Jersey
Published simultaneously in Canada

Library of Congress-in-Publication Data:

Drug metabolism in drug design and development : basic concepts and practice / edited by Donglu Zhang, Mingshe Zhu, and W. Griffith Humphreys.
p. ; cm.
Includes bibliographical references.
ISBN 978-0-471-73313-3 (cloth)
1. Drugs–Metabolism. 2. Drugs–Design. 3. Drug development.
I. Zhang, Donglu. II. Zhu, Mingshe. III. Humphreys, W. Griffith.
[DNLM: 1. Pharmaceutical Preparations–metabolism. 2. Drug Design. 3. Drug Evaluation–methods. 4. Pharmacokinetics. QV 38 D79367 2007]
RM301.55.D79 2007
615'.7–dc22

2007017661

Printed in the United States of America
10 9 8 7 6 5 4 3 2 1

DRUG METABOLISM IN DRUG DESIGN AND DEVELOPMENT

THE WILEY BICENTENNIAL–KNOWLEDGE FOR GENERATIONS

Each generation has its unique needs and aspirations. When Charles Wiley first opened his small printing shop in lower Manhattan in 1807, it was a generation of boundless potential searching for an identity. And we were there, helping to define a new American literary tradition. Over half a century later, in the midst of the Second Industrial Revolution, it was a generation focused on building the future. Once again, we were there, supplying the critical scientific, technical, and engineering knowledge that helped frame the world. Throughout the 20th Century, and into the new millennium, nations began to reach out beyond their own borders and a new international community was born. Wiley was there, expanding its operations around the world to enable a global exchange of ideas, opinions, and know-how.

For 200 years, Wiley has been an integral part of each generation's journey, enabling the flow of information and understanding necessary to meet their needs and fulfill their aspirations. Today, bold new technologies are changing the way we live and learn. Wiley will be there, providing you the must-have knowledge you need to imagine new worlds, new possibilities, and new opportunities.

Generations come and go, but you can always count on Wiley to provide you the knowledge you need, when and where you need it!

WILLIAM J. PESCE
PRESIDENT AND CHIEF EXECUTIVE OFFICER

PETER BOOTH WILEY
CHAIRMAN OF THE BOARD

PREFACE

Information on the metabolism and disposition of candidate drugs has become a critical part of all aspects of the drug discovery and development process. This comprehensive involvement of drug metabolism information has been brought about by a desire for quality design at an early stage, sometimes referred to as designing good "developability" characteristics, and then to work proactively with clinical and safety organizations to impact the design of the various development programs. This desire is driven by the need to reduce attrition rates as a means to effectively lower the cost of drug development.

Drug metabolism information in the early stages of discovery can help guide medicinal chemistry efforts toward optimization of preclinical safety and efficacy properties. This approach can be made even more effective with the active involvement of other disciplines such as pharmaceutics and toxicology. Candidates can be optimized by examining a variety of parameters beyond potency and efficacy. During the development stages drug metabolism information can help guide drug–drug interaction and special population clinical studies. Metabolism information is also critical for designing toxicology studies to that ensure the safety of metabolites is adequately tested and can also be a key part of addressing whether toxicology found in animals is likely to translate to humans.

Drug metabolism, as practiced in the pharmaceutical industry, is a multidisciplinary field that requires knowledge of analytical technologies, expertise in mechanistic and kinetic enzymology, organic reaction mechanism, pharmacokinetic analysis, animal physiology, basic chemical toxicology, preclinical pharmacology, and molecular biology. Scientists entering the field from academia often receive coursework in many of the above areas, but have usually focused the bulk of their research efforts on only one of above mentioned fields. It often requires a number of years of practice for a new scientist to gain a comprehensive understanding of all the disciplines necessary to apply drug metabolism knowledge effectively to the drug discovery and development processes.

This book offers background information as well as practical descriptions of what happens during the drug design and development process. Emphasis will be

placed on issues such as what data are needed, what experiments and analytical methods are typically employed, and how to interpret and apply data. The chapters of this book will highlight facts, detailed experimental designs, applications, and limitations of techniques.

The book was not intended to be a collection of individual reviews, rather a coherent integration of all relevant background information as well as detail of the experimental strategies and processes necessary for drug metabolism research during drug design and development. Authors aimed at providing a balanced, comprehensive perspective on their subject matter and were encouraged to include a full range of experimental approaches. The book contains four parts that should serve to integrate the entire process: Part I, Basic Concepts of Drug Metabolism; Part II, Role of Drug Metabolism in Pharmaceutical Industry; Part III, Analytical Techniques in Drug Metabolism; Part IV, Common Experimental Approaches and Protocols. This structure should provide a valuable resource to researchers seeking to broaden their knowledge of drug metabolism science as practiced in the modern pharmaceutical industry.

Donglu Zhang
Mingshe Zhu
Griff Humphreys

CONTRIBUTORS

Upendra Argikar, Metabolism and Pharmacokinetics Global Discovery Chemistry, Novartis Institutes for BioMedical Research, Inc., 250 Massachusetts Avenue, Cambridge, MA 02139 upendra.argikar@novartis.com

Suresh K. Balani, DMPK/NCDS, Millennium Pharmaceuticals, Inc., 40 Landsdowne St., Cambridge, MA 02139 suresh.balani@mpi.com

Swapan K. Chowdhury, Department of Drug Metabolism and Pharmacokinetics, Schering-Plough Research Institute, 2015 Gal-loping Hill Road, Kenilworth, NJ 07033 swapan.chowdhury@spcorp.com

S. Nilgun Comezoglu, Bristol-Myers Squibb Co., P.O. Box 4000 Mailstop: LVL F13-02, Princeton, NJ 08543 s.nilgun.comezoglu@bms.com

Renke Dai, Preclinical Research Department, Guangzhou Institute of Biomedicine and Health, Chinese Academy of Sciences, Guangzhou Science Park, China 510663 dai_renke@qibh.ac.cn

Robert Espina, Wyeth Research, 500 Arcola Road, Collegeville, PA 19426 espinaj @wyeth.com

Jinping Gan, Bristol-Myers Squibb Co., P.O. Box 4000 Mailstop: LVL MS 17-2.12, Princeton, NJ 08543 Jinping.gan@bms.com

Liang-Shang (Lawrence) Gan, Drug Metabolism and Pharmacokinetics Drug Discovery Support, Boehringer-Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, Rigdefield, CT 06877 gan@rdg.boehringer-ingelheim.com

Scott J. Grossman, Bristol-Myers Squibb Co., P.O. Box 4000 Mailstop: LVL D2-497, Princeton, NJ 08543 scott.grossman@bms.com

F. Peter Guengerich, Vanderbilt University School of Medicine, Center in Molecular Toxicology, 638 Robinson Research Building, 23rd & Pierce Avenues, Nashville, TN 37232-0146 f.guengerich@vanderbilt.edu

Thomas M. Guenther, Department of Pharmacology, College of Medicine, University of Illinois at Chicago, 835 South Wolcott Avenue, Chicago, IL 60612 tmg@uic.edu

Steven Hansel, Pfizer, Global Department of Pharmacodynamics, Dynamics, and Metabolism, 2800 Plymouth Road, Ann Arbor, Ml 48105 Steven.hansel@pfizer.com

Xiaohua Huang, Bristol Myers Squibb Co., 5 Research Parkway, Wallingford, CT 06492 xiaohua.huang@bms.com

W. Griffith Humphreys, Bristol-Myers Squibb, P.O. Box 4000 Mailstop: LVL F13-04, Princeton, NJ 08543 william.humphreys@bms.com

Susan Hurst, Pfizer, Global Department of Pharmacodynamics, Dynamics, and Metabolism, 2800 Plymouth Road, Ann Arbor, Ml 48105 susan.hurst@pfizer.com

Ramaswamy Iyer, Britstol-Myers Squibb Co., P.O. Box 4000 Mailstop: LVL F13-07, Princeton, NJ 08543 Ramaswamy.iyer@bms.com

Laurence S. Kaminsky, Laboratory of Human Toxicology and Molecular Epidemiology, Wadsworth Center, P.O. Box 509, Albany, NY 12201 kaminsky@wadsworth.org

Gang Luo, Metabolism and Pharmacokinetics, Bristol-Myers Squibb Co., 311 Pennington Rockyhill Road, Pennington, NJ 08534 gang.luo@bms.com

Shuguang Ma, Amgen, lnc., PKDM, One Amgen Center Dr, Thousand Oaks, CA 91320 sma@amgen.com

Swati Nagar, Assistant Professor, Department of Pharmaceutical Sciences, School of Pharmacy, Temple University, Philadelphia, PA 19140 swati.nagar@temple.edu

Robert Powers, University of Nebraska-Lincoln, Department of Chemistry, 722 Hamilton Hall, Lincoln, NE 68588 rpowers3@unl.edu

Rory Remmel, University of Minnesota, Dept of Medicinal Chemistry, 308 Harvard St SE, Minneapolis, MN 55455 remme001@tc.umn.edu

A. David Rodrigues, Bristol-Myers Squibb Co., P.O. Box 4000 Mailstop: LVL F14-04, Princeton, NJ 08543 david.rodrigues@bms.com

Vikram Roongta, Bristol-Myers Squibb Co., P.O. Box 4000, Princeton, NJ 08543 vikram.roongta@bms.com

Magang Shou, Amgen, Inc., Department of Pharmacokinetics and Drug Motabolism, One Amgen Center Drive, Thousand Oaks, CA 91320-1799 mshou@amgen.com

Michael W. Sinz, Bristol-Myers Squibb Co., 5 Research Parkway, Mailstop: WFD 3AB-525, Wallingford, CT 06492 michael.sinz@bms.com

Adrienne Tymiak, Bristol-Myers Squibb Co., P.O. Box 4000, Princeton, NJ 08543 Adrienne.tymiak@bms.com

Timothy S. Tracy, Department of Experimental and Clinical Pharmacology, College of Pharmacy, University of Minnesota, 7-115B Weaver-Densford Hall, 308 Harvard St. SE, Minneapolis, MN 55455 tracy017@umn.edu

Xiaoxiong "Jim" Wei, Office of Clinical Pharmacology, Food and Drug Administration, WO Bldg 21, Room 4660, 10903 New Hampshire Ave, Silver Spring, MD 20993 Xiaoxiong.wei@fda.hhs.gov

J. Andrew Williams, Pfizer, Global Department of Pharmacodynamics, Dynamics, and Metabolism, 2800 Plymouth Road, Ann Arbor, MI 48105 James Williams2@pfizer.com

Cindy Q. Xia, DMPK/NCDS, Millennium Pharaceuticals, Inc., 40 Landsdowne St., Cambridge, MA 02139 Cindy.Xia@mpi.com

Johnny J. Yang, DMPK/NCDS, Millennium Pharmaceuticals, Inc., 40 Landsdowne St., Cambridge, MA 02139 johnny.yang@mpi.com

Donglu Zhang, Bristol-Myers Squibb Co., P.O. Box 4000 Mailstop: LVL F13-09, Princeton, NJ 08543 donglu.zhang@bms.com

Hongjian Zhang, Bristol-Myers Squibb Co., P.O. Box 4000 Mailstop: LVL F13-07, Princeton, NJ 08543 hongjian.zhang@bms.com

Zhi-Yi Zhang, Drug Disposition Department, Eisal Research Institute, 4 Corporate Drive, Andover, MA 01810 zhi-yi zhang@eri.eisai.com

Weiping Zhao, Bristol-Myers Squibb Co., P.O. Box 4000 Mailstop: LVL F13-01, Princeton, NJ 08543 Weiping.zhao@bms.com

Zhoupeng Zhang, Merck & Co. Inc., 126 E. Lincoin Avenue, Rahway, NJ 07065 zhoupeng.zhang@merck.com

Mingshe Zhu, Bristol-Myers Squibb Co., P.O. Box 4000 Mailstop: LVL F13-01, Princeton, NJ 08543 mingshe.zhu@bms.com

CONTENTS