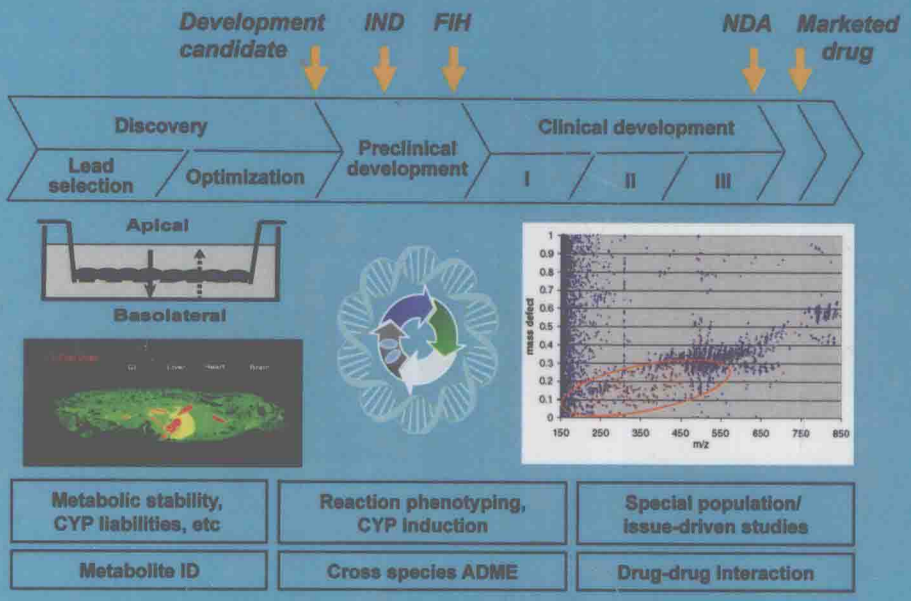
ADME-Enabling Technologies in Drug Design and Development



Edited by
DONGLU ZHANG
SEKHAR SURAPANENI

WILEY

ADME-ENABLING TECHNOLOGIES IN DRUG DESIGN AND DEVELOPMENT

EDITED BY

DONGLU ZHANG
SEKHAR SURAPANENI

WILEY
A JOHN WILEY & SONS, INC., PUBLICATION

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

Library of Congress Cataloging-in-Publication Data:
ADME-enabling technologies in drug design and development / edited by Donglu Zhang, Sekhar Surapaneni.
p. ; cm.
Includes bibliographical references and index.
ISBN 978-0-470-54278-1 (cloth)
I. Zhang, Donglu. II. Surapaneni, Sekhar.
[DNLM: 1. Drug Design. 2. Drug Evaluation, Preclinical. 3. Pharmaceutical Preparations–metabolism. 4. Pharmacokinetics. 5. Technology, Pharmaceutical–methods. QV 744]
LC-classification not assigned
615.1'9–dc23
2011030352

Printed in the United States of America.

ISBN: 9780470542781

10 9 8 7 6 5 4 3 2 1

FOREWORD

The discovery, design, and development of drugs is a complex endeavor of optimizing on three axes: efficacy, safety, and druggability or drug-likeness. Each of these axes is a potential cause of attrition as a new molecular entity progresses through the many phases of drug development. Out of the 5000–10,000 compounds evaluated in discovery efforts, only 250 enter preclinical testing, 5 enter clinical trials, and only 1 is granted approval by the Food and Drug Administration at a cost that is estimated between US$1.3–1.6 billion [1]. Efforts to increase innovation, decrease attrition, and lower the cost of drug development are the focus of the pharmaceutical industry and regulatory agencies alike. Advances have been made in some disciplines such as drug metabolism and pharmacokinetics (PK), particularly in the area of absorption, distribution, metabolism, and excretion (ADME) studies. For example, a root cause analysis of clinical attrition [2] showed that unacceptable PK or bioavailability accounted for 40% of clinical attrition in the 1990s but within a decade had been reduced to less than 10%, in large part by the identification and mitigation of risks associated with ADME/PK properties earlier in the drug discovery process. This was enabled by the introduction of automated high- and medium-throughput screening of lead optimization candidates in the discovery space. While impressive, this improvement alone is not sufficient to reverse the rising costs and long development cycle times. It is, however, a step in the right direction. As the pharmaceutical industry has evolved, the focus of ADME studies has shifted from studies conducted primarily in support of regulatory submissions to playing a significant role in the earliest stages of the discovery phase of drug development. The engagement of ADME scientists in the discovery space has allowed drug candidates to progress in the development pipeline to the next milestone with greater probability of success because desirable characteristics, such as good aqueous solubility for absorption, high bioavailability, and balanced clearance, have been engineered into the molecules, and liabilities such as high first-pass metabolism and unacceptable drug–drug interactions potential have been engineered out.

The history of the discipline of drug metabolism and PK and ADME studies, with its roots in organic chemistry and pharmacology, has been well chronicled [3–8]. The rapid advancement of the discipline over the past 50 years is clearly linked to the development of ever-increasingly sophisticated analytical tools and the growth of the pharmaceutical industry. The vast number of tools at the disposal of drug metabolism scientists has transformed the study of xenobiotics from descriptive to quantitative, *in vivo* to the molecular levels, and from simply characterizing to predicting ADME properties.

It would be beyond the scope of this introduction to provide a historical accounting of the numerous advances of technology that have shaped the field. There are, however, three noteworthy milestones in the evolution of the discipline that merit mention: the use of radioisotopes in metabolism and distribution studies; the discovery of the superfamily of drug metabolizing enzymes, the cytochrome P450s; and the revolutionizing impact of mass spectrometry as both a qualitative and quantitative tool.

With the discovery of a new radioisotope of carbon, ^{14}C, by Martin and Ruben [9], this powerful analytical tool enabled the first radiolabeled studies that elucidated the metabolic pathways and the disposition of xenobiotics in rats [10, 11]. The use of radiotracers went

on to become an indispensable tool in biochemical pathway elucidation and in drug disposition studies. While ^{14}C-labeled compounds are predominantly used in *in vivo* studies to fulfill regulatory requirement, the development of new reagents and techniques in tritium labeling now have allowed stereo- and site-selective synthesis with high specific activity, making these labeled molecule readily available for use in the earliest phases of drug discovery [12, 13].

The discovery of the cytochrome P450s and their role in the metabolism of endo- and xenobiotics opened a field of science that continues to grow and have a tremendous impact on the development of drugs and the practice of medicine. The pioneering research in this field has been well documented by Estabrook, a key contributor to our current understanding of this superfamily of enzymes [14]. The magnitude of research on the cytochrome P450s has exploded since 2003 (from greater than 2000 literature references to over 67,000 citations, as reflected by searching the PubMed database in 2011) The expanding knowledge of the cytochrome P450s has impacted early discovery efforts via assays for metabolic stability, species comparison in the selection of the most relevant species for toxicology studies, identification of the primary enzymes involved in the metabolism of a candidate drug, and potential polymorphic or drug–drug interaction liabilities of a candidate drug. The influence of the research on the cytochrome P450s also reaches into the clinical realm of drug development in the need for and design of clinical drug–drug interaction trials as well as in the regulatory guidance on drug interactions [15, 16].

No single analytical technique has had a more powerful effect on drug development than mass spectrometry, with an impact on multiple disciplines, such as chemistry, biology, and ADME [17]. An excellent review of mass spectrometry and its applications in drug metabolism and PK has recently been published [18] Mass spectrometry moved from the being a specialized tool largely used in structure identification to a "routine," but albeit powerful, analytical technology used across the pharmaceutical industry and academia alike. The selectivity, sensitivity, and speed of mass spectrometry enabled much of the success seen with high-throughput screening and advances in bioanalytical analysis in a multitude of biological matrices in both PK and biotransformation studies.

The ADME scientist of today is fortunate to have an arsenal of tools at his or her disposal, many of which will be expanded upon in this book. The advances in technologies often have implications in adjacent technologies that further the discipline of drug metabolism and PK and allow an integrated approach to solving problems and advancing drug candidates through the phases of drug development.

LISA A. SHIPLEY

REFERENCES

1. Burrill & Company. *Analysis for Pharmaceutical Research and Manufacturers of America; and Pharmaceutical Research and Manufacturers of America, PhRMA Annual Member Survey (Washington, DC: PhRMA, 2010).* Citations at http://www.phrma.org/research/infographics, 2010.
2. Kola I, Landis J (2004) Can the pharmaceutical industry reduce attrition rates? *Nature Reviews. Drug Discovery* 3:711–715.
3. Conti A, Bickel MH (1977) History of drug metabolism: Discoveries of the major pathways in the 19th century. *Drug Metabolism Reviews* 6(1):1–50.
4. Bachmann C, Bickel MH (1985) History of drug metabolism: The first half of the 20th century. *Drug Metabolism Reviews* 16(3):185–253.
5. Murphy PJ (2001) Xenobiotic metabolism: A look from the past to the future. *Drug Metabolism and Disposition* 29:779–780.
6. Murphy PJ (2008) The development of drug metabolism research as expressed in the publications of ASPET: Part 1, 1909–1958. *Drug Metabolism and Disposition* 36:1–5.
7. Murphy PJ (2008) The development of drug metabolism research as expressed in the publications of ASPET: Part 2, 1959–1983. *Drug Metabolism and Disposition* 36:981–985.
8. Murphy PJ (2008) The development of drug metabolism research as expressed in the publications of ASPET: Part 3, 1984–2008. *Drug Metabolism and Disposition* 36:1977–1982.
9. Ruben S, Kamen MD (1941) Long-lived radioactive carbon: C14. *Physical Review* 59:349–354.
10. Elliott HW, Chang FNH, Abdou IA, Anderson HH (1949) The distribution of radioactivity in rats after administration of C14 labeled methadone. *The Journal of Pharmacology and Experimental Therapeutics* 95:494–501.
11. Morris HP, Weisburger JH, Weisburger EK (1950) The distribution of radioactivity following the feeding of carbon 14-labeled 2-acetylaminofluorene in rats. *Cancer Research* 10:620–634.
12. Saljoughian M (2002) Synthetic tritium labeling: Reagents and methodologies. *Synthesis* 13:1781–1801.
13. Voges R, Heys JR, Moenius T *Preparation of Compounds Labeled with Tritium and Carbon -14*, Chichester, U.K.: John Wiley and Sons, 2009.
14. Estabrook RW (2003) A passion for P450's (remembrances of the early history of research on cytochrome P450). *Drug Metabolism and Disposition* 31:1461–1473.

15. *Guideline on the Investigation of Drug Interactions (EMA/CHMP/EWP/125211/2010)*. (2010) http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500090112.
16. *Guidance for Industry: In Vivo Drug Metabolism/Drug Interaction Studies-Study Design, Data Analysis, and Recommendations for Dosing and Labeling*. (1999) http://www.fda.gov/cder/guidance/index.htm.
17. Ackermann BL, Berna MJ, Eckstein JA, Ott LW, Chadhary AK (2008) Current applications of liquid chromatography/mass spectrometry in pharmaceutical discovery after a decade of innovation. *Annual Review Of Analytical Chemistry* 1:357–396.
18. Ramanathan R, ed. *Mass Spectrometry in Drug Metabolism and Pharmacokinetics*. Hoboken, NJ: John Wiley and Sons, 2009.

PREFACE

Understanding and characterizing absorption, metabolism, distribution, and excretion (ADME) properties of new chemical entities and drug candidates is an integral part of drug design and development. ADME is the discipline that is involved in the entire process of drug development, right from discovery, lead optimization, and clinical drug candidate selection through drug development and regulatory process. The complexity of ADME studies in drug discovery and development requires a drug metabolism scientist to know all available technologies in order to choose the right experimental approach and technology for solving the problems in a timely manner. During the last decade, tremendous progress has been made in wide array of technologies including mass spectrometry and molecular biology tools, and these enabling technologies are widely employed by ADME scientists. The generation of ADME data to support discovery and development teams is a gated process and timely generation of data to make right decisions is of paramount importance. Given the complexity of the drug discovery and development process, right techniques and tools should be used to generate timely data that is useful for decision making and regulatory filing. This requires an understanding of not only the breadth and depth of ADME technologies but also their limitation and pitfalls so scientists can make appropriate choices in employing these tools. A book on integrated enabling technologies will not only be useful to drug metabolism scientists but also could be a very helpful reference for scientists from the fields of pharmacology, medicinal chemistry, pharmaceutics, toxicology, and bioanalytical sciences in academia and industry.

This book is divided into four main sections. Part A provides the reader with an overview of ADME concepts and current topics including ADME and transporter studies in drug discovery and development, active and toxic metabolites, modeling and simulation, and developing biologics and individual medicines. Part B describes the ADME systems and methods; these include ADME screening technologies, permeability and transporter studies, distribution across specialized barriers such as blood–brain barrier (BBB) or placenta, cytochrome P450 (CYP) inhibition, induction, phenotyping, animal models for studying metabolism and transporters, and bile collection. Part C of the book discusses analytical tools including liquid chromatography-mass spectrometry (LC-MS) technologies for quantitation, metabolite identification and profiling, accelerator mass spectrometry (AMS) and radioprofiling, nuclear magnetic resonance (NMR), supercritical fluid chromatography (SFC) and other separation techniques, mass spectrometric imaging, and quantitative whole-body autoradiography (QWBA) tissue distribution techniques. Part D presents new and evolving technologies such as stem cells, genetically modified animal models, and siRNA techniques in ADME studies. Other techniques included in this section are target imaging technologies, radiosynthesis, formulation, and testing of cardiovascular toxicity potential.

We would like to thank our colleagues who are the experts and leading practitioners of the techniques described in the book for their contributions. We hope that this book is useful and serves as a quick reference to all drug hunters and to all those who are new to the discipline of ADME.

DONGLU ZHANG
SEKHAR SURAPANENI

CONTRIBUTORS

Suresh K. Balani, DMPK/NCDS, Millennium: The Takeda Oncology Company, Cambridge, MA, USA

Praveen V. Balimane, Bristol-Myers Squibb, Princeton, NJ, USA

Vanessa N. Barth, Translational Sciences, Eli Lilly and Company, Indianapolis, IN, USA

Leslie Bell, Novartis Institutes for BioMedical Research, Cambridge, MA, USA

Rajinder Bhardwaj, DMPK, Chemical Sciences and Pharmacokinetics, Lundbeck Research USA, Paramus, NJ, USA

Catherine L. Booth-Genthe, Respiratory Therapeutic Area Unit, GlaxoSmithKline, King of Prussia, PA, USA

Hong Cai, Bristol-Myers Squibb, Pennington, NJ, USA

Gamini Chandrasena, DMPK, Chemical Sciences and Pharmacokinetics, Lundbeck Research USA, Paramus, NJ, USA

Jiwen Chen, Bristol-Myers Squibb, Pennington, NJ, USA

Saeho Chong, College of Pharmacy, Seoul National University, Seoul, Korea

Lisa J. Christopher, Bristol-Myers Squibb, Princeton, NJ, USA

Jun Dai, Bristol-Myers Squibb, Princeton, NJ, USA

Li Di, Pfizer Global Research and Development, Groton, CT, USA

Ashok Dongre, Bristol-Myers Squibb, Pennington, NJ, USA

Dieter M. Drexler, Bristol-Myers Squibb, Wallingford, CT, USA

Richard W. Edom, Janssen Pharmaceutical Companies of Johnson & Johnson, Raritan, NJ, USA

Charles S. Elmore, Radiochemistry, AstraZeneca, Mölndal, Sweden

Adrian J. Fretland, Nonclinical Safety, Early ADME Department, Roche, Nutley, NJ, USA

Timothy J. Garrett, Clinical and Translational Science Institute, University of Florida, Gainesville, FL, USA

Lingling Guan, Ricerca Biosciences, Concord, OH, USA

Anshul Gupta, Drug Metabolism and Pharmacokinetics, AstraZeneca, Waltham, MA, USA

Yong-Hae Han, Bristol-Myers Squibb, Princeton, NJ, USA

Imad Hanna, Drug Metabolism and Pharmacokinetics, Novartis Institutes for BioMedical Research, East Hanover, NJ, USA

David C. Hay, MRC Centre for Regenerative Medicine, Edinburgh, UK

Haizheng Hong, College of Oceanography and Environmental Sciences, Xiamen University, Fujian, China

Cornelis E.C.A. Hop, Department of Drug Metabolism and Pharmacokinetics, Genentech, South San Francisco, CA, USA

Matthew Hoffmann, Celgene Corporation, Summit, NJ, USA

Stella Huang, Bristol-Myers Squibb, Wallingford, CT, USA

W. Griffith Humphreys, Bristol-Myers Squibb, Princeton, NJ, USA

Wenying Jian, Johnson & Johnson Pharmaceutical Research & Development, Raritan, NJ, USA

Xi-Ling Jiang, Department of Pharmaceutical Sciences, School of Pharmacy and Pharmaceutical Sciences, University at Buffalo, The State University of New York, Buffalo, NY, USA

Kim A. Johnson, Bristol-Myers Squibb, Wallingford, CT, USA

Janan Jona, Small Molecule Process and Product Development/Preformulation, Amgen Inc., Thousand Oaks, CA, USA

Elizabeth M. Joshi, Department of Drug Disposition, Lilly Research Laboratories, Indianapolis, IN, USA

Nataraj Kalyanaraman, Pharmacokinetics and Drug Metabolism, Amgen Inc., Thousand Oaks, CA, USA

Jiesheng Kang, Sanofi-Aventis U.S. Inc., Bridgewater, NJ, USA

Edward H. Kerns, Therapeutics for Rare and Neglected Diseases, NIH Center for Translational Therapeutics, Rockville, MD, USA

Yuan-Hon Kiang, Small Molecular Process and Product Development/Preformulation, Amgen Inc., Thousand Oaks, CA, USA

Wing Wah Lam, Janssen Pharmaceutical Companies of Johnson & Johnson, Raritan, NJ, USA

Chun Li, Metabolism and Pharmacokinetics, Genomics Institute of the Novartis Research Foundation, San Diego, CA, USA

Mingxiang Liao, DMPK/NCDS, Millennium: The Takeda Oncology Company, Cambridge, MA, USA

Heng-Keang Lim, Janssen Pharmaceutical Companies of Johnson & Johnson, Raritan, NJ, USA

Zhongping (John) Lin, Frontage Laboratories, Inc. Malvern, PA, USA

Chang-Xiao Liu, State Key Laboratory of Drug Technology and Pharmacokinetics, Tianjin Institute of Pharmaceutical Research, Tianjin, China

Tom Lloyd, Worldwide Clinical Trials Drug Development Solutions Bioanalytical Sciences, Austin, TX, USA

Anthony Y.H. Lu, Department of Chemical Biology, Ernest Mario School of Pharmacy, Rutgers University, Piscataway, NJ, USA

Qiang Ma, Receptor Biology Laboratory, Toxicology and Molecular Biology Branch, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Morgantown, WV, USA

Daniel P. Magparangalan, Covidien, St. Louis, MO, USA

Brad D. Maxwell, Bristol-Myers Squibb, Princeton, NJ, USA

Kaushik Mitra, Merck & Co. Inc., Rahway, NJ, USA

Voon Ong, San Diego, CA, USA

Ryan M. Pelis, Department of Pharmacology, Dalhousie University, Halifax, Nova Scotia, Canada

Natalia Penner, Department of Drug Metabolism and Pharmacokinetics, Biogen Idec, Cambridge, MA, USA

Chandra Prakash, Department of Drug Metabolism and Pharmacokinetics, Biogen Idec, Cambridge, MA, USA

Darren L. Reid, Small Molecular Process and Product Development/Preformulation, Amgen Inc., Thousand Oaks, CA, USA

Kevin L. Salyers, Pharmacokinetics and Drug Metabolism, Amgen Inc., Thousand Oaks, CA, USA

Mark Seymour, Xceleron, Heslington, York, UK

Adam Shilling, Incyte Corp, Wilmington, DE, USA

Lisa A. Shipley, Drug Metabolism and Pharmacokinetics, Merck & Co., Inc., West Point, PA, USA

Yue-Zhong Shu, Bristol-Myers Squibb, Princeton, NJ, USA

Jose Silva, Janssen Pharmaceutical Companies of Johnson & Johnson, Raritan, NJ, USA

Matthew D. Silva, Amgen Inc., Thousand Oaks, CA, USA

Sekhar Surapaneni, Drug Metabolism and Pharmacokinetics, Celgene Corporation, Summit, NJ, USA

Adrienne A. Tymiak, Bristol-Myers Squibb, Princeton, NJ, USA

Jianling Wang, Novartis Institutes for BioMedical Research, Cambridge, MA, USA

Lifei Wang, Bristol-Myers Squibb, Princeton, NJ, USA

Xiaomin Wang, Celgene Corporation, Summit, NJ, USA

David B. Wang-Iverson, Bristol-Myers Squibb, Princeton, NJ, USA

Naidong Weng, Janssen Pharmaceutical Companies of Johnson & Johnson Raritan, NJ, USA

Caroline Woodward, Department of Drug Metabolism and Pharmacokinetics, Biogen Idec, Cambridge, MA, USA

Cindy Q. Xia, Biotransformation/DMPK, Drug Safety and Disposition, Millennium: The Takeda Oncology Company, Cambridge, MA, USA

Yang Xu, Pharmacokinetics and Drug Metabolism, Amgen Inc., Thousand Oaks, CA, USA

Ming Yao, Bristol-Myers Squibb, Princeton, NJ, USA

Richard A. Yost, Department of Chemistry, University of Florida, Gainesville, FL, USA

Ai-Ming Yu, Department of Pharmaceutical Sciences, School of Pharmacy and Pharmaceutical Sciences, University at Buffalo, The State University of New York, Buffalo, NY, USA

Haoyu Zeng, Safety Assessment, Merck Research Laboratories, West Point, PA, USA

Donglu Zhang, Bristol-Myers Squibb, Princeton, NJ, USA

Yingru Zhang, Bristol-Myers Squibb, Princeton, NJ, USA

Zhoupeng Zhang, Merck & Co. Inc., Rahway, NJ, USA

Mingshe Zhu, Bristol-Myers Squibb, Princeton, NJ, USA

Peijuan Zhu, Respiratory Therapeutic Area Unit, GlaxoSmithKline, King of Prussia, PA, USA

CONTENTS