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# Drug Metabolism Prediction

**Volume 63**

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#### Series Editors

**Prof. Dr. Raimund Mannhold**

Rosenweg 7  
40489 Düsseldorf  
Germany  
[mannhold@uni-duesseldorf.de](mailto:mannhold@uni-duesseldorf.de)

**Prof. Dr. Hugo Kubinyi**

Donnersbergstrasse 9  
67256 Weisenheim am Sand  
Germany  
[kubinyi@t-online.de](mailto:kubinyi@t-online.de)

**Prof. Dr. Gerd Folkers**

Collegium Helveticum  
STW/ETH Zurich  
8092 Zurich  
Switzerland

#### Volume Editor

Dr. Johannes Kirchmair  
University of Cambridge  
Department of Chemistry  
Lensfield Road  
Cambridge, CB2 1EW  
United Kingdom

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## List of Contributors

### ***Andreas Bender***

Unilever Centre for Molecular  
Science Informatics  
Department of Chemistry  
Lensfield Road  
Cambridge CB2 1EW  
UK

### ***Jessica A. Bonzo***

Life Technologies Corporation  
Cell Biology and Stem Cell Systems  
7335 Executive Way  
Frederick, MD 21704  
USA

### ***Fabio Broccatelli***

The Institute of Cancer Research  
Division of Cancer Therapeutics  
Cancer Research UK Cancer  
Therapeutics Unit  
15 Cotswold Road  
Sutton SM2 5NG  
UK

### ***Nathan Brown***

The Institute of Cancer Research  
Division of Cancer Therapeutics  
Cancer Research UK Cancer  
Therapeutics Unit  
15 Cotswold Road  
Sutton SM2 5NG  
UK

### ***Hui Chen***

Chinese Academy of Sciences  
Institute of Chemistry  
CAS Key Laboratory of  
Photochemistry  
Beijing National Laboratory for  
Molecular Sciences (BNLMS)  
No. 2, 1st North Street,  
Zhongguancun  
Beijing 100190  
China

### ***Richard J. Dimelow***

Wright Dose Ltd  
2 Woodlands Road  
Altrincham WA14 1HF  
UK

### ***Guus Duchateau***

Unilever  
R&D Vlaardingén  
Olivier van Noortlaan 120  
3133 AT Vlaardingén  
The Netherlands

### ***Stephen S. Ferguson***

National Institute of Environmental  
Health Sciences  
Biomolecular Screening Branch  
Division of the National Toxicology  
Program  
111 T.W. Alexander Drive  
Research Triangle Park, NC 27709  
USA

**Mathew Paul Gleeson**

Kasetsart University  
Faculty of Science  
Department of Chemistry  
50 Phaholyothin Road  
Chatuchak, Bangkok 10900  
Thailand

**Natalie D. Glube**

BASF SE  
Human Nutrition Europe  
Chemiestraße 22  
68623 Lampertheim  
Germany

**Frederick Peter Guengerich**

Vanderbilt University School of  
Medicine  
Department of Biochemistry and  
Center in Molecular Toxicology  
638 Robinson Research Building  
2200 Pierce Avenue  
Nashville, TN 37232-0146  
USA

**Supa Hannongbua**

Kasetsart University  
Faculty of Science  
Department of Chemistry  
50 Phaholyothin Road  
Chatuchak, Bangkok 10900  
Thailand

**Philip Neville Judson**

Lhasa Limited  
Granary Wharf House  
2 Canal Wharf  
Leeds LS11 5PY  
UK

**Teresa Kaserer**

University of Innsbruck  
Institute of Pharmacy/  
Pharmaceutical Chemistry and  
Center for Molecular Biosciences  
Innsbruck (CMBI)  
Innrain 80–82  
6020 Innsbruck  
Austria

**Nathan J. Kidley**

Syngenta  
Jealott's Hill International Research  
Centre  
Bracknell, Berkshire RG42 6EY  
UK

**Johannes Kirchmair**

University of Cambridge  
Unilever Centre for Molecular  
Science Informatics  
Department of Chemistry  
Lensfield Road  
Cambridge CB2 1EW  
UK

and

ETH Zurich  
Institute of Pharmaceutical Sciences  
Department of Chemistry and  
Applied Biosciences  
Vladimir-Prelog-Weg 1-5/10  
8093 Zurich  
Switzerland

**Andrew G. Leach**

Liverpool John Moores University  
School of Pharmacy and  
Biomolecular Sciences  
James Parsons Building  
Byrom Street  
Liverpool L3 3AF  
UK

**Ghulam Mustafa**

Heidelberg Institute for Theoretical  
Studies  
Molecular and Cellular Modeling  
Group  
Schloss-Wolfsbrunnengasse 35  
69118 Heidelberg  
Germany

and

University of Karachi  
Dr. Panjwani Center for Molecular  
Medicine & Drug Research  
International Center for Chemical  
& Biological Sciences  
KU Circular Rd  
75270 Karachi  
Pakistan

**Chris Oostenbrink**

University of Natural Resources and  
Life Sciences  
Institute of Molecular Modeling  
and Simulation  
Muthgasse 18  
1190 Vienna  
Austria

**Oraphan Phuangsawai**

Kasetsart University  
Faculty of Science  
Department of Chemistry  
50 Phaholyothin Road  
Chatuchak, Bangkok 10900  
Thailand

**Patrik Rydberg (Deceased)**

University of Copenhagen  
Faculty of Health and Medical  
Sciences  
Department of Drug Design and  
Pharmacology  
Universitetsparken 2  
2100 Copenhagen  
Denmark

and

Optibrium Ltd  
7221 Cambridge Research Park  
Beach Drive  
Cambridge CB25 9TL  
UK

**Daniela Schuster**

University of Innsbruck  
Institute of Pharmacy/  
Pharmaceutical Chemistry and  
Center for Molecular Biosciences  
Innsbruck (CMBI)  
Innrain 80–82  
6020 Innsbruck  
Austria

**Sason Shaik**

The Hebrew University of  
Jerusalem  
Institute of Chemistry and the Lise  
Meitner-Minerva Center for  
Computational Quantum  
Chemistry  
Campus Admond Safra  
at Givat Ram  
91904 Jerusalem  
Israel

**Lu Tan**

University of Cambridge  
Cambridge Institute for Medical  
Research  
Department of Medicine  
Hills Road  
Cambridge CB2 0XY  
UK

**Veronika Temml**

University of Innsbruck  
Institute of Pharmacy/  
Pharmaceutical Chemistry and  
Center for Molecular Biosciences  
Innsbruck (CMBI)  
Innrain 80–82  
6020 Innsbruck  
Austria

**Bernard Testa**

Lausanne University Hospital  
(CHUV)  
Department of Pharmacy  
Rue du Bugnon  
1011 Lausanne  
Switzerland

**Walter Thiel**

Max-Planck-Institut für  
Kohlenforschung  
Kaiser-Wilhelm-Platz 1  
45470 Mülheim an der Ruhr  
Germany

**Simon Thomas**

Cypotex Discovery Ltd  
Scientific Computing Group  
15 Beech Lane  
Macclesfield SK10 2DR  
UK

**Dandamudi Usharani**

The Hebrew University of  
Jerusalem  
Institute of Chemistry and the Lise  
Meitner-Minerva Center for  
Computational Quantum  
Chemistry  
Campus Admond Safra  
at Givat Ram  
91904 Jerusalem  
Israel

**Rebecca C. Wade**

Heidelberg Institute for Theoretical  
Studies  
Molecular and Cellular Modeling  
Group  
Schloss-Wolfsbrunnenweg 35  
69118 Heidelberg  
Germany

and

Heidelberg University  
Center for Molecular Biology  
(ZMBH)  
Im Neuenheimer Feld 282  
69120 Heidelberg  
Germany

**Mark J. Williamson**

University of Cambridge  
Unilever Centre for Molecular  
Science Informatics  
Department of Chemistry  
Lensfield Road  
Cambridge CB2 1EW  
UK

**Ian D. Wilson**

Imperial College  
Department of Surgery and Cancer  
Exhibition Road  
South Kensington, London SW7 2AZ  
UK

**David S. Wishart**

University of Alberta  
Department of Computing Science  
2-21 Athabasca Hall  
Edmonton, AB T6G 2E8  
Canada

and

University of Alberta  
Department of Biological Sciences  
CW 405, Biological Sciences Bldg.  
Edmonton, AB T6G 2E8  
Canada

and

National Institute for  
Nanotechnology  
Division of NanoLife Sciences  
11421 Saskatchewan Drive  
Edmonton, AB T6G 2M9  
Canada

**Xiaofeng Yu**

Heidelberg Institute for Theoretical  
Studies  
Molecular and Cellular Modeling  
Group  
Schloss-Wolfsbrunnenweg 35  
69118 Heidelberg  
Germany



## Preface

In addition to mediating cell metabolism, the metabolic system developed in animals and humans for the chemical conversion of xenobiotics. Over millions of years, a plethora of oxidizing, hydrolyzing, conjugating, and other enzymes were optimized by evolution. Modification, degradation, and/or conjugation, in many cases to polar products, enable a safe elimination from the organism. Whereas many plant products are toxic, there are only rare examples that the metabolic system converts harmless natural substances into toxic entities. The situation changed about two centuries ago, after the advent of synthetic organic compounds: many of them contain structural features that the metabolic system cannot handle in the same manner as natural products. In only a few generations, evolution did not have enough time to optimize the enzymes for this new challenge. Of course, also potential drug candidates offer such a challenge to the metabolic system. The development of many compounds must be discontinued because of severe side effects of some toxic metabolites, most often chemically reactive compounds [1]. Some metabolites, even formed in only minor amounts, may cause idiosyncratic toxicity, rarely observed but with fatal consequences for the individual.

Chemical features that are easily metabolized are responsible for short biological half-life of some potential drug candidates; on the other hand, lack of such moieties might cause a half-life that is too long for safe use of the drug. In addition, such compounds as well as highly lipophilic analogs have a higher risk to form toxic metabolites. Thus, it is most important to understand metabolic pathways and to have tools to predict which compounds might be generated. This necessity applies especially for the common oxidation of xenobiotics by various cytochrome P450s (CYPs). Three approaches are suited to achieve this task: theoretical treatment, by calculating the accessibility and chemical reactivity of the chemical features of the compound; molecular modeling, especially pharmacophore searches and docking, using 3D structures of the cytochrome binding pockets; and empirical approaches, using the large databases of known metabolic pathways. All these methods have their pros and cons, and none of them seems to be perfect. Especially species selectivity, to conclude from animal results to humans, and the relative amount of certain metabolites are difficult or even impossible to predict.

The introduction of this book provides an overview of the role of metabolism in drug development, followed by a part on software and databases for the study of metabolism. The next part discusses computational approaches for the study of the most important metabolic enzymes, the cytochrome P450 enzymes. 3D structures, substrate recognition and binding, and theoretical and experimental methods for the study of ligand–protein interactions are discussed in this part. The chapters of the next part go into more detail with respect to the sites and products of metabolism, using either molecular interaction fields or structure-, reactivity-, and knowledge-based approaches. The important aspect of enzyme inhibition and induction is discussed in the next chapters, using quantitative structure–activity relationships and pharmacophore-based methods; separate chapters discuss the role of P-gp-mediated disposition and the prediction of toxic effects of metabolites. Last but not least, three chapters describe experimental approaches, that is, *in vitro* models for the study of metabolism and drug–drug interactions and experimental metabolite detection and profiling.

We are very grateful to Johannes Kirchmair for having accepted our invitation to edit this book, which will be of great importance and practical value for all scientists involved in drug research. Our thanks also go to all chapter authors for their valuable contributions, as well as to Frank Weinreich and Heike Nöthe at Wiley-VCH for their engagement in this project and in our entire book series “Methods and Principles in Medicinal Chemistry.”

Düsseldorf  
Weisenheim am Sand  
Zürich  
June 2014

*Raimund Mannhold*  
*Hugo Kubinyi*  
*Gerd Folkers*

## Reference

- 1 Kalgutkar, A.S., Dalvie, D., Obach, R.S., and Smith, D.A. (eds) (2012) *Reactive Drug Metabolites, Methods and Principles in Medicinal Chemistry*, vol. 55 (series eds R. Mannhold, H. Kubinyi, and G. Folkers), Wiley-VCH Verlag GmbH, Weinheim.

## A Personal Foreword

Metabolism is a decisive factor for the safety and performance of drugs, cosmetics, food bioactives, and agrochemicals. Methods for analyzing and predicting the metabolic fate of small molecules have become a thriving field of research during the past few years. The allure of predictive metabolism arises from its multidisciplinary nature, bringing together scientists from diverse backgrounds. The research of predictive metabolism also brought me to Cambridge, where I had the privilege to work with Robert Glen and our metabolism team, an inspiring group of a dozen scientists including bioinformaticians, chemists, computer scientists, mathematicians, pharmacists, and physicists, on new methods for predictive metabolism. Unilever and other companies supported us with the necessary funding, a platform for scientific interactions, and, most importantly, experimental data to play with. This has been a truly enlightening, collaborative environment for research and led me to further pursue this work, now together with Bayer Pharma AG at ETH Zurich.

Today a broad range of computational tools and knowledge bases for drug metabolism research are available. The vast majority of these resources are accessible to nonexpert users. With this book, we intend to provide more than a comprehensive overview of these methods and their underlying principles. Our aim is to convey expert knowledge distilled from years – decades – of experience in drug metabolism and our fascination for this field of research.

Metabolizing enzymes show a distinguished level of promiscuity for the binding of small molecules and complex and diverse reaction mechanisms. This makes assay design, readout, and interpretation extremely challenging. The importance of understanding assay and analytical technologies cannot be overemphasized. Thus, in addition to the systematic overview of prediction-based methods, in this volume four dedicated chapters will provide expert accounts of state-of-the-art experimental approaches for investigating drug metabolism, pointing out the most important caveats and common errors to consider when working with experimental data.

It was a great pleasure for me to contribute to this book with such a distinguished team of experts. I would like to take the opportunity to thank the series editors, Raimund Mannhold, Hugo Kubinyi, and Gerd Folkers, and Frank Weinreich and Heike Nöthe at Wiley-VCH for their continuous support during the

preparation of this book. I am very grateful to all contributors for their excellent work and communication.

Drug metabolism is a captivating and challenging playground for experimentalists and theoreticians alike, and there are so much more questions and challenges ahead to resolve! Thus, I hope that this book will inspire and encourage young scientists and established experts in metabolism research to further contribute to this exciting field.

On behalf of all contributors, I wish you an enjoyable and informative read.

Zurich  
June 2014

*Johannes Kirchmair*

## Part One

### Introduction





## 1

## Metabolism in Drug Development

*Bernard Testa*

## 1.1

### What? An Introduction

Drug metabolism, and more generally xenobiotic metabolism, has become a major pharmacological and pharmaceutical science with particular relevance to biology, therapeutics, and toxicology, as abundantly explained and illustrated in a number of recent books [1–8] and reviews [9–18]. As such, drug metabolism is also of great importance in medicinal chemistry and clinical pharmacology because it influences the deactivation, activation, detoxification, and toxification of most drugs [19–22]. This broader pharmacological context will be considered in Section 1.2. There, I shall address the “Why?” question, namely “Why does drug metabolism deserve so much attention?”

Given the major impact of biotransformation reactions and resulting metabolites on the preclinical and clinical success or failure of drug candidates, it comes as no surprise that huge efforts are being deployed toward developing ever earlier and faster biological tools. Here, the objective is to assess as rapidly as possible the viability of such candidates. This brings us to the “How?” question (Section 1.3), namely “How to obtain useful data and predictions on the metabolism of candidates?” Although an overview of modern analytical technologies is provided in Chapter 19 of this book, a first focus here will be on the many factors affecting the fate of a drug. Having gathered many sound if narrow experimental results, drug researchers need to make sense of them. In other words, they seek the help of artificial intelligence to extract reliable information from experimental data and transform it into valuable knowledge permitting extrapolative predictions to new molecules. This, as the reader knows, is the focus of this multi-authored book, the present chapter serving as a bird’s eye view of the field.

As much as we live in an artificial world of hardware and software, human beings, so we believe and hope, must remain masters of the game by defining objectives, being cognizant of limits, and interpreting as wisely as possible the predictions generated by machines. The point made in Section 1.4 will thus be a “Who?” question and conclusion, namely “Who among scientists are best able to assess the soundness and reliability of drug metabolism predictions?” Should

these be software specialists, chemists, biologists, or physicians? This section will end with a plea to pool competences and create teams whose total expertise will be greater than the sum of individual expertise.

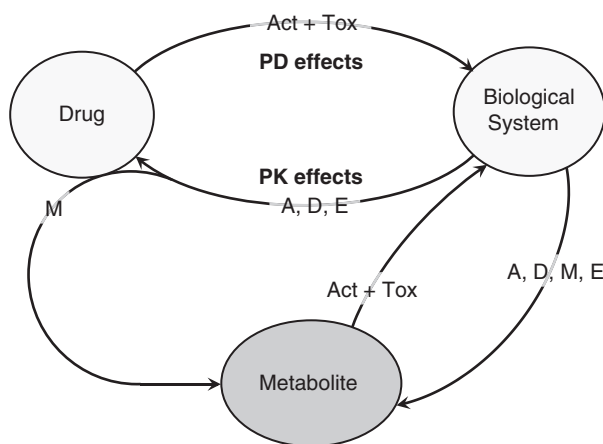
## 1.2

### Why? Metabolism in Drug Development

#### 1.2.1

##### The Pharmacological Context

To put the present book in a global context, it appears useful to ponder the fate of medicines in the body and, more specifically, in the human body. The upper part of Figure 1.1 illustrates in schematic form the two aspects of the interactions between a xenobiotic and a biological system [15,23]. Note that a “biological system” is defined here very broadly and includes functional proteins (e.g., receptors), monocellular organisms and cells isolated from multicellular organisms, isolated tissues and organs, multicellular organisms, and even populations of individuals, be they uni- or multicellular. As for the interactions between a drug (or any xenobiotic) and a biological system, they may be simplified to



**Figure 1.1** The upper part of this scheme illustrates the interaction between a drug (or any xenobiotic) and the organism (or any biological system). The salient point is the interdependence between pharmacodynamic processes (“what the drug does to the body,” namely activity (Act) and toxicity (Tox)) and pharmacokinetic processes (“what the body does to the drug,” namely absorption (A), distribution (D), metabolism

(M = biotransformation), and excretion (E)). The lower part of the scheme is meant to make explicit the potential role of metabolites in the PD effects of a drug. It emphasizes that a metabolite, once formed, will also be involved in PK processes. More important, the figure highlights the fact that metabolite(s) may also play PD roles. Such roles are two, namely pharmacological activity and/or toxic effects (modified from Ref. [23]).