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Contents

List of Contributors XV
Preface XXI
A Personal Foreword XXIII

Section 1 General Concept for Target-based Safety Assessment 1

1 Side Effects of Marketed Drugs: The Utility and Pitfalls of Pharmacovigilance 3
Steven Whitebread, Mateusz Maciejewski, Alexander Fekete, Eugen Lounkine, and László Urbán
1.1 Introduction 3
1.2 Postmarketing Pharmacovigilance 6
1.3 Polypharmacy and Pharmacological Promiscuity of Marketed Drugs 9
References 15

2 In Silico Prediction of Drug Side Effects 19
Michael J. Keiser
2.1 Large-Scale Prediction of Drug Activity 20
2.1.1 Networks of Known and New Target Activity 21
2.1.1.1 Predicting Drug Off-Targets by Statistical Chemical Similarity 21
2.1.1.2 Representing Drugs Computationally for Rapid Comparison 23
2.1.2 Resources for Multiscale Inquiry 25
2.1.2.1 Ligands to Targets 25
2.1.2.2 Perturbing Biological Systems (Phenotypes) 25
2.1.2.3 Functional and Biological Annotations (Diseases) 27
2.1.2.4 Adverse Reactions as Drug-Induced Diseases 29
2.2 Multiscale Models of Adverse Drug Reactions 30
2.2.1 Inferring Adverse Reactions 31
2.2.1.1 From Off-Targets to Antitargets 31
2.2.1.2 Systematic Antitarget Prediction and Testing 32
2.2.1.3 Finding Side Effects sans Targets 33
2.2.2 Forward Perturbation and Prediction of Mechanisms 33
5.1.2 Isoniazid – If It Were Newly Discovered, Would It Be Approved Today? 85
5.2 Special Problems of Postmarketing Hepatotoxicity 89
5.2.1 Voluntary Monitoring after Approval for Marketing 90
5.2.2 Prediction of Serious, Dysfunctional Liver Injury 90
5.2.3 Severity of Liver Injury Is Not Measured by Aminotransferase Elevations 91
5.2.4 Attempts to Standardize Terminology 91
5.2.5 What Is the “Normal” Range, or the “Upper Limit of Normal”? 92
5.2.6 Diagnostic Test Evaluation 93
5.2.7 Determination of the Likely Cause of Liver Abnormalities 94
5.2.8 Treatment and Management of DILI in Practice 95
5.3 Special Problems for New Drug Development 95
5.3.1 How Many? 95
5.3.2 How Much? 96
5.3.3 How Soon? 97
5.3.4 How Likely? 97
5.3.5 Compared with What? 97
5.3.6 ROC Curves 98
5.3.7 eDISH: Especially for Controlled Trials 99
5.3.8 Test Validation and Qualification 100
5.4 Closing Considerations 101
5.4.1 A Handful of “Do Nots” 101
5.4.2 Need to Standardize ALT Measurement and Interpretation of Normal Ranges 102
5.4.3 Research Opportunities 102
References 103

6 Mechanistic Safety Biomarkers for Drug-Induced Liver Injury 107
Daniel J. Antoine
6.1 Introduction 107
6.2 Drug-Induced Toxicity and the Liver 110
6.3 Current Status of Biomarkers for the Assessment of DILI 111
6.4 Novel Investigational Biomarkers for DILI 113
6.4.1 Glutamate Dehydrogenase (GLDH) 114
6.4.2 Acylcarnitines 115
6.4.3 High-Mobility Group Box-1 (HMGB1) 116
6.4.4 Keratin 18 (K18) 116
6.4.5 MicroRNA-122 (miR-122) 117
6.5 Conclusions and Future Perspectives 118
References 120
# In Vitro Models for the Prediction of Drug-Induced Liver Injury in Lead Discovery

Frederic Moulin and Oliver Flint

## 7.1 Introduction

## 7.2 Simple Systems for the Detection and Investigation of Hepatic Toxicants

### 7.2.1 Primary Hepatocytes

#### 7.2.1.1 Cells

#### 7.2.1.2 Cell Culture Conditions

#### 7.2.1.3 Toxicity Endpoints

#### 7.2.1.4 Limitations of Hepatocyte Cultures

### 7.2.2 Liver-Derived Cell Lines

#### 7.2.2.1 HepG2

#### 7.2.2.2 HepaRG

### 7.2.3 Differentiated Pluripotent Stem Cells

#### 7.2.3.1 Embryonic Stem Cells

#### 7.2.3.2 Induced Pluripotent Stem Cells

### 7.3 Models to Mitigate Hepatocyte Dedifferentiation

#### 7.3.1 Liver Slices

#### 7.3.2 Selective Engineering of Metabolism

### 7.4 Understanding Immune-Mediated Hepatotoxicity

#### 7.4.1 Use of Inflammatory Cofactors

#### 7.4.2 Innate Immune System and Inflammasome

### 7.5 Conclusions

## References

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# Transporters in the Liver

Bruno Stieger and Gerd A. Kullak-Ublick

## 8.1 Introduction

## 8.2 Role of Organic Anion Transporters for Drug Uptake

## 8.3 Drug Interaction with the Bile Salt Export Pump

## 8.4 Susceptibility Factors for Drug–BSEP Interactions

## 8.5 Role of BSEP in Drug Development

## References

---

# Mechanistic Modeling of Drug-Induced Liver Injury (DILI)


## 9.1 Introduction

## 9.2 Mechanistic Modules in DILIsym® version 3A

#### 9.2.1 Oxidative Stress-Mediated Toxicity

#### 9.2.2 Innate Immune Responses

#### 9.2.3 Mitochondrial Toxicity

#### 9.2.4 Bile Acid-Mediated Toxicity

## 9.3 Examples of Bile Acid-Mediated Toxicity Module

---
Section 3  Cardiovascular Side Effects  199

10  Functional Cardiac Safety Evaluation of Novel Therapeutics  201
Jean-Pierre Valentin, Brian Guth, Robert L. Hamlin, Pierre Lainée, Dusty Sarazen, and Matt Skinner
10.1 Introduction: What Is the Issue?  201
10.2 Cardiac Function: Definitions and General Principles  203
10.2.1 Definition and Importance of Inotropy and Difference from Ventricular Function  203
10.2.2 Definition and Importance of Lusitropy  207
10.2.3 Components and Importance of the Systemic Arterial Pressure  211
10.2.3.1 Afterload  212
10.3 Methods Available to Assess Cardiac Function  213
10.4 What Do We Know About the Translation of the Nonclinical Findings to Humans?  217
10.5 Risk Assessment  219
10.5.1 Hazard Identification  219
10.5.2 Risk Assessment  221
10.5.3 Risk Management  224
10.5.4 Risk Mitigation  225
10.6 Summary, Recommendations, and Conclusions  227
References  228

11  Safety Aspects of the Ca\textsubscript{v}1.2 Channel  235
Berengere Dumotier and Martin Traebert
11.1 Introduction  235
11.2 Structure of Ca\textsubscript{v}1.2 Channels  235
11.2.1 \(\alpha\)-Subunit of Ca\textsubscript{v}1.2 Channel  236
11.2.2 \(\beta\)-Subunit of Ca\textsubscript{v}1.2 Channel  236
11.3 Function of Ca\textsubscript{v}1.2 Channels in Cardiac Tissue  237
11.3.1 Role in Conduction and Contractility  239
11.3.2 Modulation of Ca\textsubscript{v}1.2 Channels  240
11.3.2.1 Voltage- and Calcium-Dependent Facilitation  241
11.3.2.2 Sympathetic Stimulation and Kinase Regulation  241
11.3.2.3 Inactivation  242
11.3.2.4 Regulation by Calmodulin  242
11.3.2.5 Indirect Regulation of Ca\textsubscript{v}1.2 Channels  243
11.3.3 Ca\textsubscript{v}1.2 and Cardiac Diseases  244
11.4 Pharmacology of Ca\textsubscript{v}1.2 Channels: Translation to the Clinic  245
11.4.1 Ca\textsubscript{v}1.2 Antagonists: Impact on Electromechanical Functions  245
11.5 Prediction of Ca\textsubscript{v}1.2 Off-Target Liability  246
11.5.1 Ca\textsubscript{v}1.2 in Cardiomyocytes Derived from iPS Cells  246
References  247
14.1.3 Simulations of the Human Cardiac AP in the Presence of hERG Blockade 303
14.1.4 Estimation of Proarrhythmic hERG Occupancy Levels Based on AP Simulations 304
14.1.5 Novel Insights about the Causes of Inadvertent hERG Binding Function 305
14.1.6 Implications of Our Findings for hERG Safety Assessment 313
14.1.7 Conclusion and Future Directions 324

References 324

Section 4 Kinase Antitargets 329

15 Introduction to Kinase Antitargets 331
Mark C. Munson
References 360

16 Clinical and Nonclinical Adverse Effects of Kinase Inhibitors 365

16.1 Introduction 365
16.2 Perspectives on the Clinical Safety of Kinase Inhibitor Therapy 371
16.3 Adverse Effects of Kinase Inhibitor Drugs 372
16.3.1 Hepatic Toxicity 372
16.3.1.1 Role of Metabolism and Clearance Pathways in Hepatotoxicity 373
16.3.1.2 Genetic Risk Factors for Hepatotoxicity 375
16.3.1.3 Preclinical Evaluation of Hepatotoxicity 376
16.3.2 Thyroid Toxicity 377
16.3.2.1 Mechanistic Basis of Thyroid Toxicity 378
16.3.2.2 Clinical Management of Thyroid Toxicity 378
16.3.3 Bone and Tooth Toxicity 379
16.3.4 Cardiovascular Toxicity 380
16.3.5 Cutaneous Toxicity 380
16.3.5.1 Mechanistic Basis of Cutaneous Toxicity 381
16.3.5.2 Preclinical Evaluation of Cutaneous Toxicity 381
16.3.5.3 Clinical Management of Cutaneous Toxicity 383
16.3.6 Developmental and Reproductive Toxicity 383
16.3.6.1 Preclinical Evaluation of Reproductive Toxicity 384
16.3.6.2 Clinical Management of Reproductive Toxicity 384
16.3.7 Gastrointestinal Toxicity 385
16.3.8 Hematopoietic Toxicity 385
16.3.8.1 Mechanistic Basis of Hematopoietic Toxicity 385
16.3.8.2 Preclinical Evaluation of Hematopoietic Toxicity 387
16.3.9 Ocular Toxicity 387
16.3.9.1 Mechanistic Basis of Ocular Toxicity 387
16.3.9.2 Preclinical Evaluation of Ocular Toxicity 388
16.3.10 Pulmonary Toxicity 388
16.3.11 Renal Toxicity 389
16.4 Derisking Strategies for Kinase Inhibitor Toxicity 389
16.5 Concluding Remarks 391
References 391

17 Cardiac Side Effects Associated with Kinase Proteins and Their Signaling Pathways 401
Roy J. Vaz and Vinod F. Patel
17.1 A Case Study 401
17.2 Introduction 402
17.3 Cardiac-Specific Kinase Antitargets 404
17.3.1 Preclinical Findings in Genetically Modified or KI-Treated Mice 404
17.3.2 Clinical Findings of Kinase Inhibitors on the Heart and Their Mechanistic Understandings 404
17.3.2.1 ErbB2 Inhibition 404
17.3.2.2 EGFR Inhibition 406
17.3.2.3 Dual EGFR/ErbB2 Inhibition 406
17.3.2.4 Raf Inhibition 407
17.3.2.5 MEK Inhibition 407
17.3.2.6 JAK/STAT Inhibition 407
17.3.2.7 Bcr–Abl Inhibition 408
17.3.2.8 PDGFR and c-Kit Inhibition 408
17.3.2.9 VEGFR Inhibition 408
17.4 Current and Future Directions 409
17.4.1 Preclinical Safety and Clinical Outcome Predictions 409
17.5 Conclusions 410
References 411

18 Case Studies: Selective Inhibitors of Protein Kinases – Exploiting Demure Features 413
Ellen R. Laird
18.1 Introduction 413
18.2 Case I: Indane Oximes as Selective B-Raf Inhibitors 414
18.3 Case II: ARRY-380 (ONT-380) – an ErbB2 Agent that Spares EGFR 420
18.4 Case III: Discovery of GDC-0068 (Ipatasertib), a Potent and Selective ATP-Competitive Inhibitor of AKT 424
18.5 Concluding Remarks 428
References 429
Section 5  Examples of Clinical Translation  435

19  Torcetrapib and Dalcetrapib Safety: Relevance of Preclinical

In Vitro and In Vivo Models  437

Eric J. Niesor, Andrea Greiter-Wilke, and Lutz Müller

19.1  Introduction  437

19.2  Effect of Torcetrapib on Blood Pressure  437

19.3  In Vitro Studies  438

19.3.1  Direct Effect of Torcetrapib on Aldosterone Production In Vitro in

Cultured H295R Adrenal Corticocarcinoma Cells  439

19.3.2  Molecular Mechanism of Torcetrapib Induction of Aldosterone

Secretion  439

19.3.3  Development of Reproducible In Vitro Screening Models for

Increase in Aldosterone and Cyp11B2 mRNA in a Human Adrenal

Corticocarcinoma Cell Line  440

19.3.4  Application of In Vitro Models for the Successful Derisking

of Dalcetrapib, Anacetrapib, and Evacetrapib  440

19.4  In Vivo Studies  441

19.4.1  Effect of Torcetrapib on Aldosterone and BP  441

19.4.1.1  Immediate Increase (Transient) in BP in Normotensive Wistar

Rats  441

19.4.1.2  Sustained Increase in BP in Spontaneously Hypertensive and Zucker

Diabetic Fatty Rats  441

19.4.1.3  Tissue mRNA Analysis Suggested Involvement of the

Renin–Angiotensin–Aldosterone System (RAAS)  442

19.4.1.4  Increase in BP and Aldosterone with Torcetrapib in All Species

Tested  443

19.4.2  Molecular Mechanisms of Torcetrapib-Induced BP

Increase  444

19.4.2.1  Torcetrapib-Positive Inotropism and Increased Cardiac Work

in a Dog Telemetry Study  446

19.4.2.2  A Common Molecular Mechanism for BP and Induction

of Aldosterone Secretion?  447

19.5  General Safety Risk with Increased Aldosterone and BP  447

19.5.1  Inappropriate Increase in Aldosterone Secretion May Increase CV

Risks  447

19.6  Relevance of BP and Aldosterone Preclinical Models to Clinical

Observation with Dalcetrapib and Anacetrapib  448

19.7  Similarities between Potent CETP inhibitors and Halogenated

Hydrocarbons  449

19.7.1  The Macrophage Scavenger Receptor MARCO, a Possible Antitarget

for Dalcetrapib, and Its Relevance to Humans  450

19.8  Conclusions  451

References  451
20

**Targets Associated with Drug-Related Suicidal Ideation and Behavior** 457
*Andreas Hartmann, Steven Whitebread, Jacques Hamon, Alexander Fekete, Christian Trendelenburg, Patrick Y. Müller, and László Urbán*

20.1 Introduction 457

20.2 Targets Associated with Increased Suicidal Intent and Behavior 458

20.2.1 G-Protein-Coupled Receptors 458
20.2.1.1 Dopamine D_{1} and D_{2} Receptors (DRD1 and DRD2) 458
20.2.1.2 Cannabinoid CB1 Receptor (CNR1) 462
20.2.1.3 Serotonin (5-HT_{1A}) Receptor (HTR1A) 464
20.2.1.4 5-HT_{2A} (HTR2A) 465

20.2.2 Transporters 466
20.2.2.1 Serotonin Transporter (SLC6A4) 466
20.2.2.2 Norepinephrine Transporter (SLC6A2) 468
20.2.2.3 Vesicular Monoamine Transporter, VMAT2 (SLC18A2) 468

20.2.3 Ion Channels 469
20.2.3.1 Neuronal Nicotinic α4β2 Channel (CHRNA4) 469
20.2.3.2 Neural-Type Voltage-Gated Calcium Channel, Ca_{v}2.2 (CACNA1B) 471

20.3 Conclusions 472
References 473

**Index** 479
List of Contributors

Daniel J. Antoine
University of Liverpool
Institute of Translational Medicine
Department of Molecular and Clinical Pharmacology
MRC Centre for Drug Safety Science
Liverpool L69 3GE
UK

Richard J. Brennan
Sanofi US
Preclinical Safety DSAR
153 2nd Ave.
Waltham, MA 02451
USA

José S. Duca
Novartis Institutes for BioMedical Research
Computer Assisted Drug Discovery
100 Technology Square
Cambridge, MA 02139
USA

Berengere Dumotier
Novartis Institutes for BioMedical Research
Preclinical Safety/Cardiac Electrophysiology
Klybeckstrasse 141, WK.136.178
4057 Basel
Switzerland

Kim L.R. Brouwer
The University of North Carolina at Chapel Hill
UNC Eshelman School of Pharmacy Division of Pharmacotherapy and Experimental Therapeutics
Chapel Hill, NC 27599
USA

Gül Erdemli
Novartis Institutes for BioMedical Research
Center for Proteomic Chemistry Ion Channel Group
250 Massachusetts Ave.
Cambridge, MA 02139
USA

Ramy Farid
Schrödinger, Inc.
120 West Forty-Fifth Street, 17th Floor
New York, NY 10036
USA
List of Contributors

Alexander Fekete
Novartis Institutes for BioMedical Research
Preclinical Safety
Preclinical Secondary Pharmacology
250 Massachusetts Avenue
Cambridge, MA 02139
USA

Oliver Flint
Bristol-Myers Squibb
Pharmaceutical Candidate Optimization
Discovery Toxicology
Liberty Drive
Newtown, PA 18940
USA

Gary Gintant
AbbVie
Integrated Science and Technology
Department of Integrative Pharmacology
Abbott Park Road
Abbott Park, IL 60064
USA

Andrea Greiter-Wilke
F. Hoffmann-La Roche Ltd.
Pharmaceuticals/Metabolic DTA
Grenzacherstrasse 124
4070 Basel
Switzerland

Robert L. Hamlin
QTest Labs LLC and The Ohio State University
1900 Coffey Road
Columbus, OH 43210
USA

Jacques Hamon
Novartis Institutes for BioMedical Research
Preclinical Safety Profiling
Klybeckstrasse 141
4057 Basel
Switzerland

Andreas Hartmann
Novartis Institutes for BioMedical Research
Preclinical Safety
Klybeckstrasse
4057 Basel
Switzerland

Brett A. Howell
The Hamner Institutes for Health Sciences
The Hamner–UNC Institute for Drug Safety Sciences
Research Triangle Park, NC 27709
USA

Daniel Hoyer
The University of Melbourne
Faculty of Medicine, Dentistry and Health Sciences
School of Medicine
Department of Pharmacology and Therapeutics
Parkville, Victoria 3010
Australia
Qi-Ying Hu
Novartis Institutes for BioMedical Research
Global Discovery Chemistry
100 Technology Square
Cambridge, MA 02139
USA

Haisong Ju
Novartis Institutes for BioMedical Research Head
Safety Pharmacology-US/Preclinical Safety
Novartis Pharmaceuticals Corporation
One Health Plaza
East Hanover, NJ 07936-1080
USA

Michael J. Keiser
University of California, San Francisco
Department of Pharmaceutical Chemistry
1700 4th Street
San Francisco, CA 94158
USA

Douglas A. Keller
Sanofi US
Preclinical Safety
DSAR
55 Corporate Dr.
Bridgewater, NJ 08807
USA

Gerd A. Kullak-Ublick
University Hospital Zurich
Department of Clinical Pharmacology and Toxicology
Raemistrasse 100
8091 Zurich
Switzerland

Pierre Lainée
Sanofi
DSAR
371, RUE DU PROF JOSEPH BLAYAC
Montpellier 34184
France
Ellen R. Laird
Array BioPharma Inc.
Computational Chemistry
3200 Walnut Street
Boulder, CO 80301
USA

Karen L. Leach
Pfizer
Centers for Therapeutic Innovation
3 Blackfan Circle
Boston, MA 02115
USA

Eugen Lounkine
Novartis Institutes for BioMedical Research
Center for Proteomic Chemistry
In Silico Lead Discovery
250 Massachusetts Avenue
Cambridge, MA 02139
USA

K. Andrew MacCannell
Novartis Institutes for BioMedical Research
100 Technology Square
Cambridge, MA 02139
USA

Mateusz Maciejewski
Novartis Institutes for BioMedical Research
Center for Proteomic Chemistry
Preclinical Safety Profiling
250 Massachusetts Avenue
Cambridge, MA 02139
USA

Frederic Moulin
Bristol-Myers Squibb
Pharmaceutical Candidate Optimization
Discovery Toxicology
Clover Lane
Madison, CT 06443
USA

Lutz Müller
F. Hoffmann-La Roche Ltd.
Pharmaceuticals/Metabolic DTA
Grenzacherstrasse 124
4070 Basel
Switzerland

Patrick Y. Müller
Novartis Pharma
Global Pharma Development Strategy
Fabrikstrasse
4057 Basel
Switzerland

Mark C. Munson
Sanofi US
LGCR-Boston Hub
153 2nd Ave
Waltham, MA, 02451
USA

Eric J. Niesor
F. Hoffmann-La Roche Ltd.
Pharmaceuticals/Metabolic DTA
Grenzacherstrasse 124
4070 Basel
Switzerland

Vinod F. Patel
Sanofi US
LGCR – Boston Hub
153 Second Avenue
Waltham, MA 02451
USA
Robert A. Pearlstein
Novartis Institutes for BioMedical Research
Computer Assisted Drug Discovery
100 Technology Square
Cambridge, MA 02139
USA

Sarita Pereira
Novartis Institutes for BioMedical Research
250 Massachusetts Avenue
Cambridge, MA 02139
USA

Dusty Sarazan
Data Sciences International
119 14th Street NW, Suite 100
St. Paul, MN 55112
USA

John R. Senior
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
USA

Lisl K. Shoda
The Hamner Institutes for Health Sciences
The Hamner–UNC Institute for Drug Safety Sciences
Research Triangle Park, NC 27709
USA

Scott Q. Siler
The Hamner Institutes for Health Sciences
The Hamner–UNC Institute for Drug Safety Sciences
Research Triangle Park, NC 27709
USA

Matt Skinner
AstraZeneca R&D
Drug Safety and Metabolism
Alderley Park
Macclesfield SK10 4TG
UK

Bruno Stieger
University Hospital Zurich
Department of Clinical Pharmacology and Toxicology
Raemistrasse 100
8091 Zurich
Switzerland

Martin Traebert
Novartis Institutes for BioMedical Research
Preclinical Safety/Cardiac Electrophysiology
Klybeckstrasse 141, WKL.136.178
4057 Basel
Switzerland

Christian Trendelenburg
Novartis Institutes for BioMedical Research
Preclinical Safety
Klybeckstrasse 141,
4057 Basel
Switzerland

¹Deceased
László Urbán  
Novartis Institutes for BioMedical Research  
Preclinical Safety  
Preclinical Secondary Pharmacology  
250 Massachusetts Avenue  
Cambridge, MA 02139  
USA  

Jean-Pierre Valentin  
UCB Biopharma  
Investigative Toxicology, Non-Clinical Development  
1420 Braine-l’Alleud  
Belgium  

Roy J. Vaz  
Sanoﬁ US  
LGCR – Boston Hub  
153 Second Avenue  
Waltham, MA 02451  
USA  

Paul B. Watkins  
The Hamner Institutes for Health Sciences  
The Hamner–UNC Institute for Drug Safety Sciences  
Research Triangle Park, NC 27709  
USA  

Steven Whitebread  
Novartis Institutes for BioMedical Research  
Preclinical Safety  
Preclinical secondary Pharmacology  
250 Massachusetts Avenue  
Cambridge, MA 02139  
USA  

Jeffrey L. Woodhead  
The Hamner Institutes for Health Sciences  
The Hamner–UNC Institute for Drug Safety Sciences  
Research Triangle Park, NC 27709  
USA  

Kyunghee Yang  
The Hamner Institutes for Health Sciences  
The Hamner–UNC Institute for Drug Safety Sciences  
Research Triangle Park, NC 27709  
USA  

Yuching Yang  
The Hamner Institutes for Health Sciences  
The Hamner–UNC Institute for Drug Safety Sciences  
Research Triangle Park, NC 27709  
USA  

The University of North Carolina at Chapel Hill  
UNC Eshelman School of Pharmacy  
Division of Pharmacotherapy and Experimental Therapeutics  
Chapel Hill, NC 27599  
USA  

and  

List of Contributors
Preface

In drug discovery, target definition and validation are the first steps, followed by the search for biologically active hits. This can be performed by “wet” screening, optimally by high-throughput techniques, or by virtual screening of large compound libraries or even much larger virtual libraries of chemical structures. Nowadays, one- or two-digit micromolar hits result in most cases and in very short time. After a search for similar compounds that might also be active, medicinal chemists start to optimize their activities against the target under consideration. Nowadays chemists are aware of the problems of “fatty” and large compounds, resulting in poor bioavailability. But a mostly unsolved problem is the optimization with respect to undesired side effects. To understand and tackle these problems, Roy Vaz and Thomas Klabunde edited 7 years ago the book “Antitargets: Prediction and Prevention of Drug Side Effects,” volume 38 of our series “Methods and Principles in Medicinal Chemistry,” in which they discussed the most important targets that might generate undesired or even fatal side effects. Now it is time to discuss some more relevant antitargets and to add recently accumulated knowledge on such targets that were already presented in the earlier volume.

We are very grateful to the editors László Urbán, Vinod F. Patel, and Roy J. Vaz, and all chapter authors for their effort to review all relevant aspects and latest developments in the field of antitarget research. Last but not least, we thank the publisher Wiley-VCH, especially Heike Nöthe, Waltraud Wüst, and Frank Weinreich, for their ongoing support of our series “Methods and Principles in Medicinal Chemistry.”

Düsseldorf
Weisenheim am Sand
Zürich
February 2015
A Personal Foreword

The concept represented by the book *Antitargets* [1] was revolutionary when it was published in 2008 with the clear intention to alert the pharmaceutical industry and the medical community to the fact that some therapeutic or unintended off-target activities could translate into serious side effects also known as adverse drug reactions (ADRs). The important message was that one needs to consider all biological effects of a drug or drug candidate, link the adverse drug reactions to molecular targets, and then devise a plan to de-risk these properties in the drug optimization phase. To a great extent, knowledge concerning ADRs has emerged from clinical side effects that were not intended when drugs were initially marketed. One of the first drugs was terfenadine (Seldane) that was withdrawn from use due to sudden deaths caused by torsades de pointes [2]. This drug in the presence of other drugs, such as ketoconazole, prolonged the cardiac QT interval due to unintended modulation of (anti-)targets, including hERG, CYP3A4/5, and P-glycoprotein, among others. The development of *in vitro* assays for these antitargets rapidly followed, and these assays were introduced into the process of drug discovery. The first book, *Antitargets*, tried to provide information on the regulatory and human clinical viewpoints, preclinical biology, pharmacology, and medicinal chemistry (structure–activity relationships (SARs)) of these antitargets. In addition, examples were included to demonstrate derisking of these antitarget activities resulting in a cleaner antitarget profile of new clinical candidates. During the writing of the first book, other antitargets emerged and were included, for example, the unexpected cardiac toxicity with 5-HT$_{2B}$ agonism on the use of the anorexigen, fenfluramine.

Black box warnings, failures in drug trials, and drug withdrawals have always been, and continue to be, part of the drug discovery and development and marketed use of drugs. Thus, a new book on antitargets has warranted to continue to capture antitarget information and knowledge not discussed previously and capture broader coverage of related, emerging topics. It is on this basis that sections in this book were assembled. Systems pharmacology, a newer field, has gained prominence and chapters dedicated to the utility in deciphering and modeling antitargets have been included in this book (see Chapters 2 and Chapter 9).
The first section deals with novel technologies and includes description of the utility of adverse event reports to drug discovery, the translational aspects of pre-clinical safety findings, broader computational prediction of drug side effects, and a description of the serotonergic system—GPCRs, enzymes, and a transporter.

The importance of hepatotoxicity in drug safety warranted several chapters solely on this subject matter. Chapter 5 starts with a view of hepatotoxicity from a clinician’s perspective. Chapter 6 includes a review of the most promising predictive biomarkers for hepatotoxicity. A description of the in vitro systems—both assays and their readouts utilized in the early phases of drug discovery—follows in Chapter 7. The role of transporters in the liver, from a pragmatic perspective, provides a deeper understanding of how drugs and their metabolites are distributed throughout the liver. As a case example (http://www.medicinenet.com/bosentan-oral/article.htm), the recent drug labeling of bosentan, resulting from the inhibition of the bile secretion export pump (BSEP) and its consequent drug-induced liver injury (DILI), is described. Finally, description of DILIsym®, an in silico approach combining known mechanisms in a mathematical framework and its application to two drugs, troglitazone and bosentan, is included.

Then follows a collection of chapters on cardiac safety and ion channels, an ever-interesting topic in toxicology. It begins with a review of inotropy and functional safety of the heart followed by updated understandings of three well-known antitarget cardiac ion channels that are important in the action potential generation in a cardiomyocyte, namely, $\mathrm{Na}_v1.5$, $\mathrm{Ca}_v1.2$, and hERG. There is an analysis of a systems pharmacology model and the latest update on hERG channel mechanisms. Also included is a chapter describing common circulating biomarkers for human subjects and preclinical species as a more sensitive method for early safety signals.

The kinase class of antitargets was not discussed in the first book and due to the numerous entries of kinase inhibitors into clinical trials a wealth of human safety data has accumulated on clinical adverse events (AEs) associated [3] with kinase inhibition. This, together with a lack of previous efforts to discuss important side effect profiles of this class of drugs, leads us to dedicate a section to kinase antitargets and their inhibitors. Chapter 15 reviews the known side effects of approved kinase inhibitors, including preclinical and clinical observations. The pharmacological and systems biology approach to understanding and predicting adverse on-mechanism effects is now being systematically applied to each of the targets, which is described in the second chapter. A chapter on cardiotoxicity and protection, specifically related to kinases and their inhibitors, is included. Application of drug discovery tools (structural biology, medicinal chemistry, and in vitro biological assays) to design safer kinase therapeutics is exemplified in the case study.

Some time ago [4], work on the anti-atherosclerotic compound torcetrapib by Pfizer was terminated, due to an increase in blood pressure. This event caused many other research efforts to pause and re-evaluate the development of drugs toward the target, cholesterylester transfer protein (CETP). As in all these types of cases, the question of on-mechanism versus off-mechanism arises. An
example of Roche’s efforts and how the question was addressed and the outcome are included in this section.

The final chapter of the book is dedicated to those compounds that inadvertently elicit CNS-mediated adverse events and lead to relabeling or withdrawal from the market. A pragmatic description of ways to mitigate these types of safety risks is provided in the last chapter.

Our deep thanks go to our contributing authors for making this book possible through their hard work, dedication, and enthusiasm.

Cambridge, MA  
Acton, MA  
Bridgewater, NJ  
February 2015

References

Section 1
General Concept for Target-based Safety Assessment