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
2.2.2.1 Forward Synthetic Behavior in Cell and Whole-Organism Model Systems 33
2.2.2.2 The Road Ahead 36
References 36

3 Translational Value of Preclinical Safety Assessment: System Organ Class (SOC) Representation of Off-Targets 45
Mateusz Maciejewski, Eugen Lounkine, Andreas Hartmann, Steven Whitebread, and László Urbán
3.1 Introduction 45
3.2 Terminology: Medicinal Dictionary for Regulatory Activities (MedDRA) 46
3.2.1 Correct Use of MedDRA Terminology at Different Phases of Drug Discovery 48
3.2.2 Determination of Symptoms Associated with a Target 50
3.3 Data Interpretation: Modifying Factors 52
3.3.1 Access to Organs 52
3.3.2 Off-Target Promiscuity: Target Interactions (Synergies and Antagonism) 53
3.4 Conclusions 53
References 54

4 Pathological Conditions Associated with the Disturbance of the 5-HT System 57
Daniel Hoyer
4.1 Introduction 57
4.2 From “St. Anthony’s Fire” to Ergot Alkaloids, the Serotonin Syndrome, and Modern 5-HT Pharmacology 59
4.3 Appetite-Reducing Agents, Fenfluramine, and Other 5-HT Releasers 61
4.4 Gastrointestinal and Antiemetic Indications, the 5-HT3/5-HT4 Receptor Links 63
4.5 Antipsychotics and the 5-HT2/Dopamine D2 Link (and Many Other 5-HT Receptors) 65
4.6 Antimigraine Medications of Old and New and the 5-HT1B/1D Receptors 67
4.7 Antidepressants/Anxiolytics Acting at 5-HT and Other Transporters 69
4.8 Conclusions 71
References 72

Section 2 Hepatic Side Effects 81

5 Drug-Induced Liver Injury: Clinical and Diagnostic Aspects 83
John R. Senior
5.1 Introduction 83
5.1.1 Postmarketing Hepatotoxicity versus Hepatotoxicity in Development 84
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
5.4.4References 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
Chapter 7: 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

Chapter 8: 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

Chapter 9: 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
9.3.1 Troglitazone and Pioglitazone 184
9.3.2 Bosentan and Telmisartan 187
9.4 Conclusions and Future Directions 190
References 191

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 Sarazan, 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\(_{\text{v}}\)1.2 Channel 235
Berengere Dumotier and Martin Traebert
11.1 Introduction 235
11.2 Structure of Ca\(_{\text{v}}\)1.2 Channels 235
11.2.1 \(\alpha\)-Subunit of Ca\(_{\text{v}}\)1.2 Channel 236
11.2.2 \(\beta\)-Subunit of Ca\(_{\text{v}}\)1.2 Channel 236
11.3 Function of Ca\(_{\text{v}}\)1.2 Channels in Cardiac Tissue 237
11.3.1 Role in Conduction and Contractility 239
11.3.2 Modulation of Ca\(_{\text{v}}\)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\(_{\text{v}}\)1.2 Channels 243
11.3.3 Ca\(_{\text{v}}\)1.2 and Cardiac Diseases 244
11.4 Pharmacology of Ca\(_{\text{v}}\)1.2 Channels: Translation to the Clinic 245
11.4.1 Ca\(_{\text{v}}\)1.2 Antagonists: Impact on Electromechanical Functions 245
11.5 Prediction of Ca\(_{\text{v}}\)1.2 Off-Target Liability 246
11.5.1 Ca\(_{\text{v}}\)1.2 in Cardiomyocytes Derived from iPS Cells 246
References 247
12  Cardiac Sodium Current (Na\textunderscore 1.5) 253  
    
   12.1  Background and Scope 253  
   12.2  Structure and Function 255  
   12.2.1  Molecular Biology 255  
   12.2.2  SCN5A Mutations Related to Congenital Long QT Syndromes 256  
   12.2.3  Evidence for Multiple Functional Types of Cardiac Sodium Channels and Heterogeneous Distribution 257  
   12.3  Physiological Role and Drug Actions 258  
   12.3.1  Fast Sodium Current (I\textsubscript{NaF}): Conduction and Refractoriness 258  
   12.3.2  Late (or Residual or Slow) Sodium Current (I\textsubscript{NaL}) 259  
   12.3.3  Drug Effects on I\textsubscript{NaF} 261  
   12.3.3.1  Voltage-Dependent Block 262  
   12.3.3.2  Use-Dependent Block (and Tonic Block) 262  
   12.3.3.3  Models of Block and Classification Schemes Based on Antiarrhythmic Drug Effects 263  
   12.3.4  Indirect Modulation of I\textsubscript{NaF} 264  
   12.4  Methodology 265  
   12.4.1  Use of Human Stem Cell-Derived Cardiomyocytes 266  
   12.5  Translation of Effects on I\textsubscript{NaF}: Relation to Conduction Velocity and Proarrhythmia 268  
   12.6  Conclusions 269  

References 270  

13  Circulating Biomarkers for Drug-Induced Cardiotoxicity: Reverse Translation from Patients to Nonclinical Species 279  
   
   13.1  Introduction 279  
   13.2  Cardiac Troponins 280  
   13.3  Natriuretic Peptides 282  
   13.4  Novel/Exploratory Biomarkers: H-FABP, miRNA, and Genomic Biomarkers 285  
   13.5  Regulatory Perspective 286  
   13.6  Conclusions and Future Perspectives 288  

References 289  

14  The Mechanistic Basis of hERG Blockade and the Proarrhythmic Effects Thereof 295  
    
   14.1  Introduction 295  
   14.1.1  The Role of hERG Dysfunction/Blockade in Promoting Early After Depolarizations 296  
   14.1.2  The Dynamics of hERG Blockade 301  

References 295
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
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 CETPi 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 D1 and D2 Receptors (DRD1 and DRD2) 458
20.2.1.2 Cannabinoid CB1 Receptor (CNR1) 462
20.2.1.3 Serotonin (5-HT1A) Receptor (HTR1A) 464
20.2.1.4 5-HT2A (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, Ca2.2 (CACNA1B) 471
20.3 Conclusions 472
References 473

Index 479