CONTENTS

Preface to the Second Edition xvii
Preface to the First Edition xix
List of Contributors xxi

1 Overview of Drug Transporter Families 1
Guofeng You and Marilyn E. Morris

1.1 What Are Drug Transporters? 1
1.2 Structure and Model of Drug Transporters 1
1.3 Transport Mechanisms 2
1.4 Polarized Expression of Drug Transporters in Barrier Epithelium 2
1.5 Classifications of Drug Transporters 2
   1.5.1 Definition of Efflux and Influx Transporters 2
   1.5.2 Definition of Absorptive and Secretory Transporters 2
   1.5.3 Relationship between Influx/Efflux and Absorptive/Secretory Transporters 2
   1.5.4 ABC Transporters and SLC Transporters 4
1.6 Regulation of Drug Transporters 4
References 4

2 Organic Cation and Zwitterion Transporters (OCTs, OCTNs) 7
Hermann Koepsell

2.1 Introduction 7
2.2 hOCT1 (SLC22A1), hOCT2 (SLC22A2), and hOCT3 (SLC22A3) 7
   2.2.1 Basic Functional Properties of OCT1–3 8
   2.2.2 Structure and Proposed Transport Mechanism of OCT1–3 9
   2.2.3 Comparison of Substrate and Inhibitor Selectivities of hOCT1–3 11
   2.2.4 Distribution of hOCT1 11
   2.2.5 Regulation of hOCT1 11
   2.2.6 Physiological and Biomedical Roles of hOCT1 14
   2.2.7 Pathological Implications of hOCT1 and Therapeutical Aspects 15
   2.2.8 Distribution of hOCT2 15
   2.2.9 Regulation of hOCT2 15
   2.2.10 Physiological and Biomedical Roles of hOCT2 15

References
3 Organic Anion Transporters

Kevin T. Bush, Megha Nagle, David M. Traong, Vibha Bhatnagar, Gregory Kaler, Sattish A. Eraly, Wei Wu and Sanjay K. Nigam

3.1 OAT Family
   3.1.1 Introduction
   3.1.2 Discovery
   3.1.3 Nomenclature

3.2 Molecular Characterization
   3.2.1 Genomics
   3.2.2 Protein Structure
   3.2.3 Mechanism of Substrate Translocation

3.3 Expression and Regulation of OATs
   3.3.1 Tissue Distribution
   3.3.2 Ontogeny
   3.3.3 Transcriptional Regulation
   3.3.4 Posttranslational Regulation

3.4 OAT Substrates
   3.4.1 Substrates
   3.4.2 Substrate Specificity
   3.4.3 Inhibitors

3.5 Systems Biology of OATs
   3.5.1 Physiological Role
   3.5.2 Pathophysiological Role
   3.5.3 Clinical Pharmacology
   3.5.4 Remote Communication, Sensing and Signaling

3.6 Conclusions
Acknowledgments
References

4 Organic Anion-Transporting Polypeptides

Rommel G. Tirrona and Richard B. Kim

4.1 Introduction to the OATP Superfamily
   4.1.1 Introduction
   4.1.2 Nomenclature

References
4.2 Molecular Characteristics of OATPs
4.2.1 Gene Structure
4.2.2 Protein Structure
4.2.3 Transport Mechanisms
4.3 Expression and Regulation of OATPs
4.3.1 Tissue Distribution
4.3.2 Posttranslational Regulation
4.3.3 Adapter Protein Interactions
4.3.4 Transcriptional Regulation
4.4 OATP Substrates and Inhibitors
4.4.1 Substrates
4.4.2 Substrate Specificity of Human OATPs
4.4.3 Inhibitors
4.5 Pharmacology of OATPs
4.5.1 Pharmacogenetics
4.5.2 Drug Interactions
4.6 Physiological/Pathophysiological Roles
4.6.1 Bilirubin Homeostasis
4.6.2 Thyroid Hormone Homeostasis
4.6.3 Bile Acid Homeostasis
4.6.4 Steroid Hormone Homeostasis
4.6.5 Prostaglandin Homeostasis
4.6.6 Cancer
4.6.7 Other Associations with Disease
4.7 Conclusions
Acknowledgments
References

5 Peptide Transporters
Stephen M. Carl, Dea Herrera-Ruiz, Rajinder K. Bhardwaj, Olafur Gudmundsson and Gregory T. Knipp

5.1 Introduction
5.2 Molecular and Structural Characteristics
5.3 Functional Properties
5.3.1 Mechanism of Transport
5.3.2 Molecular Requirements for Substrate Recognition and Transport
5.3.3 General Substrate Specificities
5.3.4 Established Endogenous and Exogenous Substrates
5.4 Regulation
5.4.1 Dietary Regulation
5.4.2 Developmental Regulation
5.4.3 Regulation by Circadian Rhythms
5.4.4 Disease State–Dependent Regulation
5.4.5 Hormonal Regulation
5.4.6 Regulation by Pharmaceutical Agents
5.4.7 Single Nucleotide Polymorphisms
5.4.8 Splice Variants
5.5 Pharmaceutical Drug Screening
5.5.1 Case Study: Targeting Peptide Transporters for Increased Oral Absorption
5.6 Concluding Remarks
Acknowledgments
References

6 Monocarboxylic Acid Transporters
Zejian Lin and Lester R. Drewes

6.1 Introduction
6.2 Mitochondrial Pyruvate Transporter Family
6.3 SLC5 Transporter Family
   6.3.1 Structure
   6.3.2 Location and Function
   6.3.3 Pharmaceutical Substrates and Disease

6.4 SLC16 Transporter Family
   6.4.1 Introduction
   6.4.2 Functional Roles of MCTs under Physiological Conditions and in Drug Transport
   6.4.3 Regulation of MCTs Activity

References

7 The Nucleoside Transporters CNTs and ENTs

Horace T. B. Ho and Joanne Wang

7.1 Introduction

7.2 Molecular and Functional Characteristics of CNTs (SLC28)
   7.2.1 Family Members and Substrate Specificity
   7.2.2 Transport Mode of CNTs
   7.2.3 Tissue Distribution and Cellular Localization of CNTs
   7.2.4 Interaction with Nucleoside Analogs
   7.2.5 Structure–Function Relationship of CNTs

7.3 Molecular and Functional Characteristics of ENTs (SLC29)
   7.3.1 Family Members and Substrate Specificity
   7.3.2 Transport Mode of ENTs
   7.3.3 Tissue Distribution and Cellular Localization of ENTs
   7.3.4 Interaction with Nucleoside Analogs
   7.3.5 Structure–Function Relationship of ENTs

7.4 Regulation of CNT and ENT Nucleoside Transporters

7.5 Physiological and Pathophysiological Functions of CNTs AND ENTs
   7.5.1 Nucleoside Homeostasis
   7.5.2 Adenosine Signaling
   7.5.3 ENT3 in Autosomal Recessive Disorders
   7.5.4 Physiological Function of PMAT/ENT4

7.6 Therapeutic Significance of CNTs and ENTs
   7.6.1 CNTs and ENTs in Intracellular Disposition of Nucleoside Drugs
   7.6.2 CNTs and ENTs in Pharmacokinetics of Nucleoside Drugs
   7.6.3 CNTs and ENTs as Drug Targets

7.7 Conclusions and Future Directions

Acknowledgment

Abbreviations

References

8 Bile Salt Transporters

Jyrki J. Eloranta, Bruno Stieger and Gerd A. Kullak-Ublick

8.1 Overview of the Enterohepatic Circulation of Bile Salts
8.2 The Chief Transporters in the Enterohepatic Circulation of Bile Salts
8.3 Enterohepatic Bile Salt Transporters in Liver Disease
8.4 Control of Bile Salt Transport and Metabolism
8.5 Nuclear Receptors as Transcriptional Regulators of Bile Salt Homeostasis
   8.5.1 FXR: The Master Regulator of Bile Salt Transport and Homeostasis
   8.5.2 The Role of PXR and VDR as Bile Salt Sensors
   8.5.3 The Bile Salt-Induced Transcriptional Repressor SHP

8.6 FXR-Dependent Mechanisms That Regulate Human Bile Salt Transporter Genes
   8.6.1 Positive Feedback Control of Bile Salt Efflux Systems by Bile Salts
   8.6.2 Negative Feedback Control of Bile Salt Uptake Systems by Bile Salts
   8.6.3 Impact of Genetic Variants of FXR on Bile Salt Homeostasis
9 Multidrug Resistance Protein: P-Glycoprotein

Adam T. Clay and Frances J. Sharom

9.1 The P-Glycoprotein Gene Family
9.2 Tissue Distribution of P-Glycoprotein
9.3 Role of P-Glycoprotein in Human Physiology
9.4 P-Glycoprotein Substrates and Modulators
9.5 P-Glycoprotein Structure
9.6 Subcellular Systems for Studying P-Glycoprotein
9.7 ATP Binding and Hydrolysis by P-Glycoprotein
9.8 Drug Binding by P-Glycoprotein
9.9 P-Glycoprotein-Mediated Drug Transport
9.10 Substrate Specificity of P-Glycoprotein and the Nature of the Drug-Binding Site
9.11 P-Glycoprotein as a Hydrophobic Vacuum Cleaner or Drug Flippase
9.12 Role of the Lipid Bilayer in P-Glycoprotein Function
9.13 Mechanism of Action of P-Glycoprotein
9.14 Role of P-Glycoprotein in Drug Therapy
9.15 Modulation of P-Glycoprotein in Cancer Treatment
9.16 Regulation of P-Glycoprotein Expression
9.17 P-Glycoprotein Gene Polymorphisms and Their Implications in Drug Therapy and Disease
9.18 Summary and Conclusions

References

10 Multidrug Resistance Proteins of the ABCC Subfamily

Anne T. Nies and Thomas Lang

10.1 Introduction
10.2 Molecular Characteristics
10.3 Functional Properties, Substrate Specificity, and Multidrug Resistance Profiles of Human ABCC/MRPs
10.4 Localization of ABCC/MRP Efflux Transporters in Normal Human Tissues and in Human Cancers
10.4.1 ABCC1
10.4.2 ABCC2
10.4.3 ABCC3
10.4.4 ABCC4
10.4.5 ABCC5
10.4.6 ABCC6
10.4.7 ABCC10, ABCC11, and ABCC12
10.5 Genotype–Phenotype Correlations and Clinical Consequences of Genetic Variants in ABCC Genes
10.5.1 Genetic Variants of Human ABCC/MRP Genes and the Mendelian Inheritance of Diseases and Syndromes
10.5.2 Genetic Variants of Human ABCC/MRP Genes and Clinical Consequences on Drug Response and Susceptibility to Complex Disease
10.6 Conclusions and Future Prospects
Acknowledgments
References

11 Breast Cancer Resistance Protein (BCRP) or ABCG2

Agnes Basseville, Robert W. Robey, Julian C. Bahr and Susan E. Bates

11.1 Discovery and Nomenclature
11.2 ABCG2 Gene and Expression
11.2.1 The ABCG2 Gene
11.2.2 Factors Controlling ABCG2 Expression
## 11.3 Physical Properties
- 11.3.1 Structure
- 11.3.2 Trafficking and Regulation of Cell Surface Expression

## 11.4 Substrates/Inhibitors of ABCG2
- 11.4.1 Endogenous Substrates
- 11.4.2 Exogenous Substrates
- 11.4.3 Inhibitors

## 11.5 Recent Findings in Physiological Function
- 11.5.1 ABCG2, Urate, and Gout
- 11.5.2 Jr(a−) Phenotype

## 11.6 Predicted Physiological Function from Tissue Distribution
- 11.6.1 Stem Cells
- 11.6.2 Placenta
- 11.6.3 Mammary Gland
- 11.6.4 Testis
- 11.6.5 Blood–Brain Barrier
- 11.6.6 Liver and the Gastrointestinal Tract
- 11.6.7 Kidneys

## 11.7 ABCG2 Expression in Cancer and Its Role in Drug Resistance

## 11.8 Genetic Polymorphisms
- 11.8.1 Inventory
- 11.8.2 Q141K and Drug Disposition/Clinical Outcome
- 11.8.3 Other Polymorphisms and Drug Disposition/Clinical Outcome

## 11.9 Conclusion

## References

## 12 Multidrug and Toxin Extrusion Proteins
*Stephen H. Wright*

### 12.1 Introduction
- 12.1.1 MATE Activity in the Context of the Cellular Physiology of Renal and Hepatic Organic Cation Secretion
- 12.1.2 The Cellular Basis of Renal OC Secretion

### 12.2 Tissue and Subcellular Distribution of MATEs

### 12.3 Functional Characteristics of MATE Transporters

### 12.4 Kinetics and Selectivity of MATE-Mediated Transport
- 12.4.1 Kinetics
- 12.4.2 Selectivity

### 12.5 Molecular/Structural Characteristics of MATE Transporters

### 12.6 Regulation of MATE and Activity

### 12.7 Influence of MATEs on Renal OC Clearance and Clinical Drug–Drug Interactions

### 12.8 Conclusions

##Acknowledgments

## References

## 13 Drug Transport in the Liver
*Brian C. Ferslew, Kathleen Kdock and Kim L. R. Brouwer*

### 13.1 Hepatic Physiology: Liver Structure and Function

### 13.2 Hepatic Uptake Transport Proteins

### 13.3 Hepatic Efflux Transport Proteins
- 13.3.1 Canalicular Transport Proteins
- 13.3.2 Basolateral Efflux Transport Proteins

### 13.4 Regulation of Hepatic Drug Transport Proteins
- 13.4.1 Transcriptional Regulation
- 13.4.2 Posttranslational Regulation
13.5 Disease State Alterations in Hepatic Transport Proteins
13.5.1 Cholestasis
13.5.2 Dubin–Johnson Syndrome
13.5.3 Rotor Syndrome
13.5.4 Nonalcoholic Steatohepatitis
13.5.5 Inflammation and Inflammation-Induced Cholestasis
13.5.6 Human Immunodeficiency Virus (HIV) Infection
13.5.7 Chronic Hepatitis C Virus (HCV) Infection
13.6 Model Systems for Studying Hepatobiliary Drug Transport
13.6.1 \textit{In Vitro} Systems
13.6.2 \textit{In Vivo} Systems
13.7 Drug Interactions in Hepatobiliary Transport
13.8 Interplay between Drug Metabolism and Transport
13.9 Hepatic Transport Proteins as Determinants of Drug Toxicity
13.10 The Future of Hepatic Drug Transport
Acknowledgments
References

14 Drug Transport in the Brain
Tamima Ashraf, Patrick T. Ronaldson and Reina Bendayan

14.1 Introduction
14.2 Physiology of the Brain Barriers and Brain Parenchyma
14.2.1 Blood–Brain Barrier
14.2.2 Cellular Compartments of the Neurovascular Unit and Brain Parenchyma
14.2.3 Blood–Cerebrospinal Fluid Barrier
14.3 Functional Expression of Drug Transporters in the Brain
14.3.1 ATP-Binding Cassette Drug Efflux Transporters
14.3.2 Solute Carrier (SLC) Drug Transporters
14.4 Relevance of Drug Transporters in CNS Disorders
14.4.1 Brain Tumors
14.4.2 Brain HIV-1 Infection
14.4.3 Epilepsy
14.4.4 Neurodegenerative Diseases
14.4.5 Cerebral Hypoxia and Ischemic Stroke
14.4.6 Pain
14.5 Regulation of Drug Transporters by Nuclear Receptors in the Brain
14.6 Conclusion
References

15 Drug Transport in the Kidney
Hiroyuki Kusuhara, Takashi Sekine, Naohiko Anzai and Hitoshi Endo

15.1 Introduction
15.2 Families of Renal Drug Transporters
15.2.1 Organic Anion Transporter Family (OAT Family Encoded by \textit{SLC22})
15.2.2 Organic Anion-Transporting Peptide (OATP) Family (\textit{SLCO})
15.2.3 Organic Cation Transporter (OCT) Family (\textit{SLC22})
15.2.4 OCTN/Carnitine Transporter Family
15.2.5 Multidrug and Toxin Extrusion Family (\textit{SLC47})
15.2.6 Peptide Transporter (PEPT) Family (\textit{SLC15})
15.2.7 Sodium/Phosphate Transporter Type 1 (NPT1) Family (\textit{SLC17})
15.2.8 \textit{Na}⁺-Coupled Concentrative Nucleoside Transporter (CNT/\textit{SLC28}) and Equilibrative Nucleoside Transporter (ENT/\textit{SLC29})
15.2.9 MDR1/P-Glycoprotein (\textit{ABCB1})
15.2.10 Multidrug Resistance-Associated Protein (MRP) Family (ABCC) 310
15.2.11 Breast Cancer Resistance Protein (BCRP) (ABCG2) 310
15.3 Regulation of Renal Drug Transporters 310
15.3.1 Phosphorylation 310
15.3.2 Glycosylation 311
15.3.3 Protein–Protein Interaction 311
15.3.4 Gender and Developmental Differences 311
15.3.5 Epigenetic Regulation 311
15.4 Pharmacokinetic and Pharmacological/Toxicological Aspects 312
15.4.1 Pharmacokinetic Aspects 312
15.4.2 Toxicological Aspects 314
15.4.3 Pharmacogenomics of Drug Transporters 315
15.5 In Vitro Model Systems for Studying Renal Drug Transport 315
15.6 FDA and EMA Draft Guidance/Guideline for Drug–Drug Interaction Studies 316
15.7 Perspectives 316
References 316

16 Drug Transporters in the Intestine 327

Patrick J. Sinko

16.1 Introduction 327
16.2 Intestinal Drug Permeation 327
16.2.1 Transcellular Diffusion 328
16.2.2 Paracellular Transport 329
16.2.3 Transcytosis 329
16.3 Drug Transporters in the Small Intestine 329
16.4 Impact of Small Intestinal Transporters on Oral Absorption of Drugs 331
16.4.1 PepT1-Mediated Absorptive Transport 332
16.4.2 OATP-Mediated Absorptive Transport 332
16.4.3 P-gp-Mediated Secretory Transport 333
16.4.4 BCRP-Mediated Secretory Transport 334
16.4.5 Intestinal Basolateral Transporters 334
16.5 Functional Modulation of Intestinal Transporters to Optimize Oral Absorption of Drugs 335
16.6 Concluding Remarks 335
References 335

17 Drug Transport in the Placenta 341

Qingcheng Mao, Vadivel Ganapathy and Jashvant D. Unadkat

17.1 Introduction 341
17.2 Blood–Placental Barrier Relevant to Drug Permeability and Transport 341
17.3 Drug Transporters in Human Placenta 342
17.3.1 ABC Transporters in Human Placenta 342
17.3.2 SLC Transporters in Human Placenta 345
17.4 Methods to Study Placental Drug Transport 348
17.5 Summary 349
References 350

18 Experimental Approaches to the Study of Drug Transporters 355

Yoshiyuki Kubo, Akira Tsuji and Yukio Kato

18.1 Introduction 355
18.2 In Vivo Experiments 355
18.2.1 Preparation of Knockout Mice 355
18.2.2 In Vivo RNA Interference 356
18.2.3 Comparative Study of Wild-Type and Knockout/Knockdown Mice 356
CONTENTS xv

18.2.4 Humanized Mice 357
18.2.5 In Vivo Imaging 358

18.3 Isolated Tissue Methods 358
18.3.1 Loop Method 358
18.3.2 Ussing-Type Chamber 358
18.3.3 Everted Sac Method 359
18.3.4 Sliced Organs 359

18.4 Primary Cell Cultures and Established Model Cell Lines 359
18.4.1 Isolated Hepatocytes 359
18.4.2 Fibroblasts 359
18.4.3 Established Cell Lines 360
18.4.4 Transfected Cell Lines and Xenopus laevis Oocytes 360
18.4.5 Techniques to Study Cellular Uptake or Transport 361

18.5 Membrane Vesicles 362
18.5.1 Membrane Vesicles from Cultured Cells 362
18.5.2 Membrane Vesicles from Tissues 362
18.5.3 Rapid Filtration Technique 362

18.6 Analysis of Drug Interaction Mechanisms 363
18.6.1 Inhibition Studies 363
18.6.2 Elucidation of Regulatory Mechanisms 363

18.7 Perspectives 364
References 365

19 Transporters in Drug Discovery: In Silico Approaches 371
Ayman El-Kattan, Manthena V. Varma and Yurong Lai

19.1 Introduction 371
19.2 Physicochemical Determinants of Hepatobiliary Elimination 371
19.3 In Silico Models for Biliary Excretion 373
19.4 Physicochemical Determinants of Renal Elimination 375
19.5 In Silico Models of Renal Excretion 375
19.6 Physicochemical Determinants of Brain Penetration 376
19.7 In Silico Approaches and SAR of Clinical Relevant Transporters 377
19.7.1 MDR1 P-gp 377
19.7.2 MRP2 378
19.7.3 BCRP 379
19.7.4 OATPs 380
19.7.5 OATs and OCTs 381
19.8 Strategies to Assess Transporter Involvement during Drug Discovery 381
19.9 Conclusions 382
References 382

20 Polymorphisms of Drug Transporters and Clinical Relevance 389
Aparna Chhibber, Janine Micheli and Deanna L. Kroetz

20.1 Genetic Variation and Drug Response 389
20.2 Genetic Variation in Membrane Transporters 390
20.3 Functional Analysis of Transporter Variants 391
20.3.1 Coding Variants 391
20.3.2 Noncoding Variants 393
20.4 Clinical Significance of Transporter Variants 394
20.4.1 Endogenous Substrates 394
20.4.2 Drugs and Other Xenobiotic Substrates 396
20.4.3 Future Directions 397
References 398
21 Diet/Nutrient Interactions with Drug Transporters

Xiaodong Wang and Marilyn E. Morris

21.1 Introduction

21.2 Diet/Nutrient Interactions with Drug Transporters

21.2.1 Interactions of Diet/Dietary Supplements with Drug Transporters

21.2.2 Interactions of Flavonoids with Drug Transporters

21.3 Conclusions

Acknowledgments

References

22 Clinical Relevance: Drug–Drug Interactions, Pharmacokinetics, Pharmacodynamics, and Toxicity

Serena Marchetti and Jan H. M. Schellens

22.1 Introduction

22.2 Interactions Mediated by ABC Drug Transporters

22.2.1 ABCB1 (MDR1, P-Glycoprotein, Pgp)

22.2.2 ABCG2 (Breast Cancer Resistance Protein, BCRP)

22.2.3 ABCC Family (Multidrug Resistance-Associated Proteins, MRP1–MRP9)

22.3 Interactions Mediated by Organic Anion and Cation Transporters (Solute Carrier Family, SLC22)

22.3.1 Organic Anion Transporters (OATs)

22.3.2 Organic Anion-Transporting Polypeptides (OATPs)

22.3.3 Organic Cation Transporters (OCTs)

22.3.4 Organic Cation/Ergothioneine/Carnitine Transporters (OCTNs)

22.4 Interactions Mediated by Peptide Transporters (PEPTs, SLC15)

22.4.1 Pharmacological and Toxicological Function

22.4.2 Drug–Drug Interactions

22.5 Interactions Mediated by Multidrug and Toxin Extrusion Transporters (MATEs, SLC47)

22.5.1 Pharmacological and Toxicological Functions

22.5.2 Drug–Drug Interactions

22.6 Interactions Mediated by Monocarboxylate Transporters (MCTs, SLC16)

22.6.1 Pharmacological and Toxicological Function

22.6.2 Drug–Drug Interactions

22.7 Interactions Mediated by Nucleoside (Concentrative and Equilibrative) Transporters (CNTs/ENTs, SLC28/29)

22.7.1 Pharmacological and Toxicological Function

22.7.2 Drug–Drug Interactions

22.8 Conclusions

References

23 Regulatory Science Perspectives on Transporter Studies in Drug Development

Sue-Chih Lee, Lei Zhang and Shiew-Mei Huang

23.1 Introduction

23.2 Regulatory Science Perspectives on Transporter Studies

23.2.1 The FDA Guidance on Evaluation of Transporter-Mediated Drug Interactions

23.2.2 Overview of the FDA Guidance to Industry Pertaining to Transporters

23.2.3 Emerging Transporters in Drug–Drug Interactions and Drug-Induced Toxicities

23.2.4 Practical Considerations in Transporter Studies

23.3 Recent FDA NDA Review Examples

23.4 Conclusion and Future Directions

Acknowledgments

Abbreviation List

References

Index