Contents

List of Contributors XIX Preface XXIX A Personal Foreword XXXI

Part I Transversal Issues Concerning Animal Models in Drug Discovery 1

۱v

1	The 3Ns of Preclinical Animal Models in Biomedical Research 3
	José Miguel Vela, Rafael Maldonado, and Michel Hamon
1.1	First N: The Need for Use of Animal Models 3
1.2	Second N: The Need for Better Animal Models 5
1.2.1	Unbiased Design 8
1.2.2	Comprehensive Reporting 8
1.2.3	Selection of the Animal Model Based on Its Validity Attributes 9
1.2.4	Appropriate Time and Dosing 11
1.2.5	Use of Biomarkers 12
1.2.6	Use of Various Animal Models 13
1.2.7	Quantitative, Multiple, and Cross-Predictive Measurements 14
1.2.8	Pharmacokinetic–Pharmacodynamic Integration 15
1.2.9	Predefinition and Adherence to the Desired Product Profile 16
1.2.10	Comparison with Gold Standard References 18
1.2.11	Reverse Translation/Backtranslation (Bedside-to-Bench
	Approach) 18
1.3	Third N: The Need for 3Rs Guiding Principles 19
	References 22
2	Alternative Models in Drug Discovery and Development Part I:
	In Silico and In Vitro Models 27
	Luz Romero and José Miguel Vela
2.1	Introduction 27
2.2	In Silico Models 34
2.2.1	Quantitative Structure–Activity Relationship 34
2.2.2	Biokinetic Modeling 37

VI Contents

2.2.3	Disease- and Patient-Specific In Silico Models 42
2.3	In Vitro Models 43
2.3.1	Primary Cells, Cell Lines, Immortalized Cell Lines, and Stem Cells 44
2.3.2	Advanced In Vitro Models for the Prediction of Drug Toxicity 46
2.3.3	In Vitro Tumor Models 47
	References 50
3	Alternative Models in Drug Discovery and Development Part II:
5	In Vivo Nonmammalian and Exploratory/Experimental
	Human Models 59
	Luz Romero and José Miguel Vela
3.1	Introduction 59
3.2	In Vivo Nonmammalian Models 59
3.2.1	Zebrafish 61
3.2.2	D. melanogaster 66
3.2.2	
	C. elegans 71
3.3	In Vivo Exploratory and Experimental Human Models 74
3.3.1	Phase 0 (Exploratory Human Models): Microdosing Studies 76
3.3.2	Phase IB/IIA (Proof-of-Concept) Studies: Experimental Human
	Models 81
	References 84
	Fabiant lanuar and Descriptions and Cuidelines Concerning
4	Ethical Issues and Regulations and Guidelines Concerning Animal Research 91
	David Sabaté
4.1	
4.1	Introduction 91
4.2	Current Use of Animals in Biomedical and Pharmaceutical
4.2	Research 92
4.3	Ethical Concerns and Positions on Animal Research 93
4.4	General Principles for the Ethical Use of Animals in Research 95
4.4.1	The 3Rs Principles (Replacement, Reduction, and Refinement) 95
4.4.2	The Principle of Justification 96
4.4.3	The Principle of Responsibility 97
4.5	Regulatory Framework for Use of Animals in Research 98
4.5.1	European Union 98
4.5.2	The United States 100
4.5.3	Canada 100
4.5.4	Japan 100
4.5.5	Australia 101
4.5.6	India 101
4.5.7	China 101
4.5.8	Brazil 102
4.5.9	Countries without a Specific Legal Framework 102
	Acknowledgment 102
	References 102
	References 102

5 Regulatory Issues: Safety and Toxicology Assessment 10
--

Antonio Guzmán

- 5.1 Introduction 107
- 5.1.1 Animal Testing 107
- 5.1.2 Regulatory Context 109
- Clinical Context 109 5.1.3
- 5.2 Animal Species in Toxicology Studies 110
- 5.2.1 Rodents 111
- 5.2.2 Nonrodents 112
- 5.2.3 Nonconventional Animal Models 114
- 5.3 Toxicology Studies 114
- General Principles 114 5.3.1
- 5.3.2 General and Repeated Dose Toxicity Studies 116
- 5.3.3 Safety Pharmacology 118
- 5.3.4 Genotoxicity 119
- 5.3.5 Development and Reproductive Toxicity Studies 122
- Carcinogenicity Studies 124 5.3.6
- Translation to Clinics: Limitations and Difficulties 126 5.4 References 127

Generation and Use of Transgenic Mice in Drug Discovery 131 6

Guillaume Pavlovic, Véronique Brault, Tania Sorg, and Yann Hérault

- 6.1 Introduction 131
- 6.2 Improved Mouse Genetic Engineering 133
- 6.2.1 Recent Technical Developments 133
- The Advent of New Mouse Mutant Resource: 6.2.2 One Stop Shop 133
- 6.3 Functional Evaluation and Uses of Mouse Models 136
- 6.3.1 Standardization and Harmonization 136
- 6.3.2 Genetic Background and Environmental Influences 137
- 6.3.3 Challenges Ahead 137
- 6.3.4 Target Identification and Translation to Humans 138
- 6.3.5 Use of GEMMs in Pharmaceutical Industry and Risk Assessment 139
- 6.4 Translation to Clinics: Limitations and Difficulties 140
- 6.5 Perspectives 142
 - Acknowledgments 143
 - References 143

7 In Vivo Brain Imaging in Animal Models: A Focus on PET and MRI 149 Fabien Chauveau, Mathieu Verdurand, and Luc Zimmer

- 7.1 Introduction: Role of Animal in In Vivo Imaging 149
- 7.1.1 In Vivo Imaging as a Translational Approach for Basic Research 149
- 7.1.2 In Vivo Imaging in Animal Models in the Pharmaceutical Industry 150
- 7.1.3 In Vivo Imaging in Animal Models and the 3R Principles 150

VIII Contents

7.2	The Choice of the Right Imaging Modality for Brain Imaging 151
7.3	Small Animal Magnetic Resonance Imaging 152
7.3.1	Principles 152
7.3.2	Magnetic Resonance Spectroscopy 152
7.3.3	Magnetic Resonance Imaging 153
7.4	Positron Emission Tomography 155
7.4.1	Basic Principles and Instrumentation 155
7.4.2	PET and Neuronal Metabolism 155
7.4.3	PET and Brain Receptors and Transporters 156
7.4.4	PET and Receptor Occupancy 158
7.4.5	PET and Neurotransmitter Release 159
7.5	Clinical Translation: Limitations and Difficulties 159
7.5.1	Anesthesia 160
7.5.2	Spatial Resolution and Sensitivity 160
7.5.3	The Mass Effect of Injected Tracers 161
7.5.4	Multimodal PET-MRI for Better Clinical Translation 162
	References 163

Part II Animal Models in Specific Disease Areas of Drug Discovery 167

8	Substance Abuse and Dependence 169
	Elena Martín-García, Patricia Robledo, Javier Gutiérrez-Cuesta, and
	Rafael Maldonado
8.1	Introduction 169
8.2	Difficulties to Model Addiction in Animals 170
8.3	Tolerance, Sensitization, and Physical Withdrawal 172
8.3.1	Tolerance 172
8.3.2	Sensitization 173
8.3.3	Physical Manifestations of Withdrawal 174
8.3.4	Affective Manifestations of Withdrawal 175
8.4	Reward and Reinforcement 177
8.4.1	Drug Discrimination 177
8.4.2	Conditioned Place Preference 178
8.4.3	Intracranial Self-Stimulation 180
8.4.4	Self-Administration 182
8.5	Translation to Clinics: Limitations and Difficulties 184
	References 186
9	Mood and Anxiety Disorders 193
	Guy Griebel and Sandra Beeské
9.1	Introduction 193
9.2	Animal Models of Anxiety Disorders 194
9.2.1	Preclinical Measures of Anxiety 194
9.2.2	Preclinical Anxiety Models and Endophenotypes 195
9.3	Animal Models of Mood Disorders 197

9.3.1 Major Depressive Disorder 197 Preclinical Measures of Depression 9.3.1.1 198 Endophenotype Models of Depression 199 9.3.1.2 9.3.2 Bipolar Disorder 199 9.4 Translation to Clinics: Limitations and Difficulties 200 Acknowledgment 201 References 202 10 Schizophrenia 207 Ronan Depoortère and Paul Moser 10.1 Introduction 207 Models Amenable to Use in Screening 209 10.2 Models Based on the Use of Pharmacological Agents 10.2.1 209 10.2.1.1 Dopaminergic Agonists 209 10.2.1.2 NMDA/Glutamate Receptor Antagonists 211 10.2.1.3 Other Pharmacological Agents Used to Induce Behavioural Changes 212 10.2.1.4 5-HT_{2A} Receptor Agonists 212 10.2.1.5 Cannabinoid Receptor Agonists 212 10.2.1.6 Muscarinic Receptor Antagonists 213 Glycine B Receptor Antagonists 213 10.2.1.7 Models Not Based on the Use of Pharmacological Agents 213 10.2.2 10.2.2.1 Conditioned Avoidance Response 213 10.2.2.2 Potentiation of PPI of the Startle Reflex 214 10.2.3 Models More Time Consuming and/or Difficult to Implement 214 10.2.3.1 Models Aimed at Reproducing More Complex Symptoms of Schizophrenia 214 Models Aimed at Reproducing the Chronic Nature of 10.2.3.2 Schizophrenia 216 Models Based on Genetic Manipulations 10.2.3.3 218 10.2.4 Models for Side Effects 218 Models for Motor Side Effects 219 10.2.4.1 Hyperprolactinemia 220 10.2.4.2 10.2.4.3 Sedation and Motor Incoordination 220 10.2.4.4 Models for Cognitive Side Effects 220 Metabolic Disorders Models 221 10.2.4.5 Models for Cardiovascular Effects 221 10.2.4.6 Translation to the Clinic: Limitations and Difficulties 221 10.3 10.3.1 Use of "Standard Subjects" 221 10.3.2 From Here to . . . ? 222 References 223 11 Migraine and Other Headaches 231 Inger Jansen-Olesen, Sarah Louise T. Christensen, and Jes Olesen Introduction 231 11.1 Vascular Models 231 11.2

X Contents

l		
	11.2.1	In Vitro 232
	11.2.2	In Vivo 233
	11.3	Neurogenic Inflammation 234
	11.4	Nociceptive Activation of the Trigeminovascular System 234
	11.4.1	Electrophysiological Recordings on Primary Dural Afferents in Trigeminal Ganglion 237
	11.4.2	Electrophysiological Recordings in Trigeminal Nucleus Caudalis 239
	11.4.3	Histological Markers after Nociceptive Stimulation of the Trigeminovascular System 239
	11.5	Cortical Spreading Depression 240
	11.6	Human Experimental Migraine Provoking Models 241
	11.7	Animal Experimental Migraine Provoking Models 242
	11.8	Transgenic Models 246
	11.9	Behavioral Models 246
	11.9.1	Allodynia or Hyperalgesia 247
	11.9.2	Face Grooming 248
	11.9.3	Photophobia 248
	11.9.4	Various Behaviors 249
	11.10	Translation to Clinics: Limitations and Difficulties 249
		References 250
	12	Nociceptive, Visceral, and Cancer Pain 261
		Christophe Mallet, Denis Ardid, and David Balayssac
	12.1	Introduction 261
	12.2	Acute Pain Tests 261
	12.2.1	Introduction 261
	12.2.2	Electrical Stimulus 263
	12.2.3	Thermal Stimulus 264
	12.2.4	Mechanical Stimulus 264
	12.2.5	Chemical Stimulus 265
	12.3	Visceral Pain Models 265
	12.3.1	Introduction 265
	12.3.2	Pain Achievement Test 266
	12.3.3	Animal Models 267
	12.3.4	Pathophysiology and Pharmacology 269
	12.4	Cancer Pain Models 270
	12.4.1	Introduction 270
	12.4.2	Pain Assessment in Animal Models of Cancer Pain 270 Animal Models 271
	12.4.3	
	12.4.4 12.4.5	Pathophysiology and Pharmacology 272 Conclusions 272
	125	
	12.5 12.5 1	Translation to Clinics: Difficulties and Limitations 273
	12.5.1	Acute Pain Tests 273

- 12.5.3 Cancer Pain Models 274
- 12.5.4 Conclusions 275 References 275
- 13 Inflammatory, Musculoskeletal/Joint (OA and RA), and Postoperative Pain 283
 - Laurent Diop and Yassine Darbaky
- 13.1 Introduction: Evaluation of Pain in Animal Models 283
- 13.2 Inflammatory Pain 287
- Formalin Test 287 13.2.1
- 13.2.2 Carrageenan-Induced Hyperalgesia 287
- Complete Freund's Adjuvant-Induced Hyperalgesia 288 13.2.3
- 13.2.4 Capsaicin-Induced Hyperalgesia 288
- 13.3 Musculoskeletal/Joint Osteoarthritis (OA) and Rheumatoid Arthritis (RA) Pain 289
- 13.3.1 Osteoarthritis Pain Models 289
- Rheumatoid Arthritis Pain Models 293 13.3.2
- 13.4 Postoperative Pain 297
- 13.4.1 Incisional Pain 298
- Laparotomy 299 13.4.2
- Ovariohysterectomy 299 13.4.3
- Other Models of Postoperative Pain 299 13.4.4
- Translation to Clinics: Limitations and Difficulties 300 13.5 References 302
- 14 Neuropathic Pain 305
 - Said M'Dahoma, Sylvie Bourgoin, and Michel Hamon
- Introduction 305 14.1
- 14.2 Main Types of Neuropathic Pain in Humans 306
- 14.2.1 Neuropathic Pain Caused by Peripheral Nerve Lesions 306
- Diabetes-Induced Neuropathic Pain 306 14.2.1.1
- Human Immunodeficiency Virus-Related Pain 14.2.1.2 306
- 14.2.1.3 Postherpetic Neuralgia 307
- Neuropathic Pain Caused by Anticancer Drugs 307 14.2.1.4
- 14.2.2 Neuropathic Pain Caused by Central Lesions 307
- Spinal Cord Injury 307 14.2.2.1
- The Various Types of Pain in SCI Patients 308 14.2.2.2
- 14.3 Modelization of Chronic Pain in Rodents 309
- 14.3.1 Models of Peripheral Nerve Injury 309
- 14.3.1.1 Nerve Section 309
- 14.3.1.2 Nerve Ligation, Compression, and Other Lesion Procedures 310
- Drug- and Virus-Induced Neuropathic Pain 314 14.3.1.3
- 14.3.2 Models of Spinal Cord Injury 318
- Spinal Cord Contusion 318 14.3.2.1
- 14.3.2.2 Clip Compression Injury 319

XII Contents

14.3.2.3	Spinal Cord Transection 319
14.3.2.4	Spinal Cord Ischemia 319
14.3.3	Neuropathic-Like Pain Evoked by Chemicals Administered at the Spinal Level <i>320</i>
14.3.3.1	Intrathecal Administration of ATP 320
14.3.3.2	Intrathecal Administration of BDNF 320
14.3.3.3	Excitotoxic Injury to the Spinal Cord 321 Translation to Clinics: Limitations and Difficulties 321
14.4	References 324
15	Obesity and Metabolic Syndrome 333
	Sunil K. Panchal, Maharshi Bhaswant, and Lindsay Brown
15.1	Introduction 333
15.2	Why Metabolic Syndrome? 333
15.3	Classical Animal Models of Obesity and Metabolic Syndrome 335
15.3.1	Genetic Models of Obesity and Diabetes 336
15.3.2	Artificially Induced Metabolic Syndrome in Animals 337
15.3.2.1	Monosodium Glutamate-Induced Obesity 338
15.3.2.2	Intrauterine Growth-Restricted Rats 338
15.4	Human Experimental Models 344
15.5	Translation to Clinics: Difficulties and Limitations 344
1010	References 344
16	Cognitive Disorders: Impairment, Aging, and Dementia 349
16	Cognitive Disorders: Impairment, Aging, and Dementia 349 Nick P. van Goethem, Roy Lardenoije, Konstantinos Kompotis
16	Nick P. van Goethem, Roy Lardenoije, Konstantinos Kompotis,
	Nick P. van Goethem, Roy Lardenoije, Konstantinos Kompotis, Bart P.F. Rutten, Jos Prickaerts, and Harry W.M. Steinbusch
16.1	Nick P. van Goethem, Roy Lardenoije, Konstantinos Kompotis, Bart P.F. Rutten, Jos Prickaerts, and Harry W.M. Steinbusch Introduction 349
	Nick P. van Goethem, Roy Lardenoije, Konstantinos Kompotis, Bart P.F. Rutten, Jos Prickaerts, and Harry W.M. Steinbusch Introduction 349 Pharmacological Models 349
16.1 16.2 16.2.1	Nick P. van Goethem, Roy Lardenoije, Konstantinos Kompotis, Bart P.F. Rutten, Jos Prickaerts, and Harry W.M. Steinbusch Introduction 349 Pharmacological Models 349 Inhibition of Energy/Glucose Metabolism 350
16.1 16.2 16.2.1 16.2.2	Nick P. van Goethem, Roy Lardenoije, Konstantinos Kompotis, Bart P.F. Rutten, Jos Prickaerts, and Harry W.M. Steinbusch Introduction 349 Pharmacological Models 349 Inhibition of Energy/Glucose Metabolism 350 Cholinergic Interventions 350
16.1 16.2 16.2.1	Nick P. van Goethem, Roy Lardenoije, Konstantinos Kompotis, Bart P.F. Rutten, Jos Prickaerts, and Harry W.M. Steinbusch Introduction 349 Pharmacological Models 349 Inhibition of Energy/Glucose Metabolism 350 Cholinergic Interventions 350 Glutamatergic Antagonists 352
16.1 16.2 16.2.1 16.2.2 16.2.3	Nick P. van Goethem, Roy Lardenoije, Konstantinos Kompotis, Bart P.F. Rutten, Jos Prickaerts, and Harry W.M. Steinbusch Introduction 349 Pharmacological Models 349 Inhibition of Energy/Glucose Metabolism 350 Cholinergic Interventions 350 Glutamatergic Antagonists 352 Serotonergic Intervention 353
16.1 16.2 16.2.1 16.2.2 16.2.3 16.2.4	Nick P. van Goethem, Roy Lardenoije, Konstantinos Kompotis, Bart P.F. Rutten, Jos Prickaerts, and Harry W.M. Steinbusch Introduction 349 Pharmacological Models 349 Inhibition of Energy/Glucose Metabolism 350 Cholinergic Interventions 350 Glutamatergic Antagonists 352 Serotonergic Intervention 353 Aging and Transgenic Models 353
16.1 16.2 16.2.1 16.2.2 16.2.3 16.2.4 16.3	Nick P. van Goethem, Roy Lardenoije, Konstantinos Kompotis, Bart P.F. Rutten, Jos Prickaerts, and Harry W.M. Steinbusch Introduction 349 Pharmacological Models 349 Inhibition of Energy/Glucose Metabolism 350 Cholinergic Interventions 350 Glutamatergic Antagonists 352 Serotonergic Intervention 353
16.1 16.2 16.2.1 16.2.2 16.2.3 16.2.4 16.3 16.3.1	Nick P. van Goethem, Roy Lardenoije, Konstantinos Kompotis, Bart P.F. Rutten, Jos Prickaerts, and Harry W.M. Steinbusch Introduction 349 Pharmacological Models 349 Inhibition of Energy/Glucose Metabolism 350 Cholinergic Interventions 350 Glutamatergic Antagonists 352 Serotonergic Intervention 353 Aging and Transgenic Models 353 Normal Aging 354
16.1 16.2 16.2.1 16.2.2 16.2.3 16.2.4 16.3 16.3.1 16.3.2	Nick P. van Goethem, Roy Lardenoije, Konstantinos Kompotis, Bart P.F. Rutten, Jos Prickaerts, and Harry W.M. Steinbusch Introduction 349 Pharmacological Models 349 Inhibition of Energy/Glucose Metabolism 350 Cholinergic Interventions 350 Glutamatergic Antagonists 352 Serotonergic Intervention 353 Aging and Transgenic Models 353 Normal Aging 354 Alzheimer's Disease 355 Parkinson's Disease 358
16.1 16.2 16.2.1 16.2.2 16.2.3 16.2.4 16.3 16.3.1 16.3.2 16.3.3	Nick P. van Goethem, Roy Lardenoije, Konstantinos Kompotis, Bart P.F. Rutten, Jos Prickaerts, and Harry W.M. Steinbusch Introduction 349 Pharmacological Models 349 Inhibition of Energy/Glucose Metabolism 350 Cholinergic Interventions 350 Glutamatergic Antagonists 352 Serotonergic Intervention 353 Aging and Transgenic Models 353 Normal Aging 354 Alzheimer's Disease 355 Parkinson's Disease 358
16.1 16.2 16.2.1 16.2.2 16.2.3 16.2.4 16.3 16.3.1 16.3.2 16.3.3 16.3.4	Nick P. van Goethem, Roy Lardenoije, Konstantinos Kompotis, Bart P.F. Rutten, Jos Prickaerts, and Harry W.M. Steinbusch Introduction 349 Pharmacological Models 349 Inhibition of Energy/Glucose Metabolism 350 Cholinergic Interventions 350 Glutamatergic Antagonists 352 Serotonergic Intervention 353 Aging and Transgenic Models 353 Normal Aging 354 Alzheimer's Disease 355 Parkinson's Disease 358 Frontotemporal Dementia 359
$16.1 \\ 16.2 \\ 16.2.1 \\ 16.2.2 \\ 16.2.3 \\ 16.2.4 \\ 16.3 \\ 16.3.1 \\ 16.3.2 \\ 16.3.3 \\ 16.3.4 \\ 16.3.5 $	Nick P. van Goethem, Roy Lardenoije, Konstantinos Kompotis, Bart P.F. Rutten, Jos Prickaerts, and Harry W.M. Steinbusch Introduction 349 Pharmacological Models 349 Inhibition of Energy/Glucose Metabolism 350 Cholinergic Interventions 350 Glutamatergic Antagonists 352 Serotonergic Intervention 353 Aging and Transgenic Models 353 Normal Aging 354 Alzheimer's Disease 355 Parkinson's Disease 358 Huntington's Disease 358 Frontotemporal Dementia 359
$16.1 \\ 16.2 \\ 16.2.1 \\ 16.2.2 \\ 16.2.3 \\ 16.2.4 \\ 16.3 \\ 16.3.1 \\ 16.3.2 \\ 16.3.3 \\ 16.3.4 \\ 16.3.5 \\ 16.3.6 \\ 16.3.6 \\ 100000000000000000000000000000000000$	Nick P. van Goethem, Roy Lardenoije, Konstantinos Kompotis, Bart P.F. Rutten, Jos Prickaerts, and Harry W.M. Steinbusch Introduction 349 Pharmacological Models 349 Inhibition of Energy/Glucose Metabolism 350 Cholinergic Interventions 350 Glutamatergic Antagonists 352 Serotonergic Intervention 353 Aging and Transgenic Models 353 Normal Aging 354 Alzheimer's Disease 355 Parkinson's Disease 358 Huntington's Disease 358 Frontotemporal Dementia 359 Down Syndrome 360
$16.1 \\ 16.2 \\ 16.2.1 \\ 16.2.2 \\ 16.2.3 \\ 16.2.4 \\ 16.3 \\ 16.3.1 \\ 16.3.2 \\ 16.3.3 \\ 16.3.4 \\ 16.3.5 \\ 16.3.6 \\ 16.3.6 \\ 100000000000000000000000000000000000$	Nick P. van Goethem, Roy Lardenoije, Konstantinos Kompotis, Bart P.F. Rutten, Jos Prickaerts, and Harry W.M. Steinbusch Introduction 349 Pharmacological Models 349 Inhibition of Energy/Glucose Metabolism 350 Cholinergic Interventions 350 Glutamatergic Antagonists 352 Serotonergic Intervention 353 Aging and Transgenic Models 353 Normal Aging 354 Alzheimer's Disease 355 Parkinson's Disease 358 Frontotemporal Dementia 359 Down Syndrome 360 Translation to Clinics: Limitations and Difficulties 360
$16.1 \\ 16.2 \\ 16.2.1 \\ 16.2.2 \\ 16.2.3 \\ 16.2.4 \\ 16.3 \\ 16.3.1 \\ 16.3.2 \\ 16.3.3 \\ 16.3.4 \\ 16.3.5 \\ 16.3.6 \\ 16.4$	Nick P. van Goethem, Roy Lardenoije, Konstantinos Kompotis, Bart P.F. Rutten, Jos Prickaerts, and Harry W.M. Steinbusch Introduction 349 Pharmacological Models 349 Inhibition of Energy/Glucose Metabolism 350 Cholinergic Interventions 350 Glutamatergic Antagonists 352 Serotonergic Intervention 353 Aging and Transgenic Models 353 Normal Aging 354 Alzheimer's Disease 355 Parkinson's Disease 358 Huntington's Disease 358 Frontotemporal Dementia 359 Down Syndrome 360 Translation to Clinics: Limitations and Difficulties 360 References 362

- 17.2 Stroke Models 368
- 17.2.1 Global Stroke Models 368
- 17.2.2 Focal Stroke Models 369
- 17.2.2.1 Extravascular Models 369
- 17.2.2.2 Photothrombosis Model 370
- 17.2.2.3 Intraluminal Occlusion Model 370
- 17.2.2.4 Thromboembolic Models 370
- 17.3 Traumatic Brain Injury Models 371
- 17.3.1 TBI Models with Craniotomy 372
- 17.3.1.1 Weight-Drop Model 372
- 17.3.1.2 Lateral Fluid Percussion Model 372
- 17.3.1.3 Controlled Cortical Impact Model 372
- 17.3.2TBI Models without Craniotomy372
- 17.3.2.1 Weight-Drop Model 373
- 17.3.2.2 Impact/Acceleration Model 373
- 17.3.2.3 Acceleration/Deceleration Model 373
- 17.3.3 Blast Injury Models 373
- 17.3.4 Repetitive TBI Models 374
- 17.4 Outcome Assessment 375
- 17.5 Translation to Clinics: Limitations and Difficulties 377
- 17.5.1 The Actual Target: From the Neuron to the Neurogliovascular Unit *377*
- 17.5.2 From Bench to Bedside to Bench: Recommendations for Improving the Translational Research 378 References 379

18 Movement Disorders: Parkinson's Disease 387

Houman Homayoun and Christopher G. Goetz

- 18.1 Introduction 387
- 18.1.1 Parkinson's Disease 387
- 18.2 Drug- and Toxin-Based Models of PD 389
- 18.2.1 Reserpine 389
- 18.2.2 Haloperidol 390
- 18.2.3 6-OHDA 390
- 18.2.4 MPTP 393
- 18.2.5 Rotenone 396
- 18.2.6 Paraquat and Other Environmental Toxins 398
- 18.3 Genetic and Functional Models of PD 398
- 18.3.1 Rodent Genetic Models 399
- 18.3.1.1 Adult-Onset Rodent Gene-Based Models 401
- 18.3.2 Rodent Function-Based Models 403
- 18.3.3 Nonrodent Genetic Models of PD 404
- 18.4 Translation to Clinics: Limitations and Difficulties 405 References 409

XIV Contents

19	Epilepsy: Animal Models to Reproduce Human Etiopathology 415 Isabelle Guillemain, Christophe Heinrich, and Antoine Depaulis
19.1	Introduction 415
19.2	What Animal Species to Use to Model Epilepsy? 416
19.3	Which Type of Models Provide the Most Reliable Information on the Pathophysiology of Epilepsies? <i>417</i>
19.4	Modeling Four Prototypic Forms of Epilepsy 418
19.4.1	Idiopathic Generalized Epilepsies with Convulsive Seizures 418
19.4.2	Idiopathic Generalized Epilepsies with Absence Seizures 419
19.4.3	Focal Epilepsies Associated with Cortical Dysplasia 420
19.4.4	Modeling Focal Epilepsies Associated with Hippocampal Sclerosis 422
19.5	Translation to Clinics: Limitations and Difficulties 423 References 425
20	Lung Diseases 431
	Laurent Boyer, Armand Mekontso-Dessap, Jorge Boczkowski, and Serge Adnot
20.1	Introduction 431
20.2	Animal Models of Lung Emphysema or Chronic Obstructive
	Pulmonary Disease 432
20.2.1	Cigarette Smoke-Induced COPD 432
20.2.2	COPD Induced by Tracheal Elastase Instillation 433
20.2.3	Genetically Modified Models of COPD 434
20.2.4	Conclusions 434
20.3	Animal Models of Pulmonary Hypertension 434
20.3.1	Relevance of Experimental Animal Models of PH to Human PH 435
20.3.2	The Monocrotaline Model of Pulmonary Hypertension 436
20.3.3	Fawn-Hooded Rats 437
20.3.4	Hypoxic PH 437
20.3.5	SU5416 Treatment Combined with Hypoxia in Mice 438
20.3.6	PH Related to COPD or Smoke Exposure 439
20.4	Animal Models of Fibrotic Lung Diseases 439
20.4.1	Bleomycin-Induced Pulmonary Fibrosis 439
20.4.2	Other Models 440
20.5	Animal Models of Acute Respiratory Distress Syndrome 440
20.6	Translation to Clinics: Limitations and Difficulties 445
	References 446
21	Heart Failure 449
	Jin Bo Su and Alain Berdeaux
21.1	Introduction 449
21.2	Hypertension-Related Heart Failure 450
21.3	Pressure and Volume Overload-Induced Heart Failure 452
21.3.1	Pressure Overload-Induced Heart Failure 452
21.3.2	Volume Overload-Induced Heart Failure 454

Contents XV

		Conte
21.3.3	Double Pressure and Volume Overload-Induced Heart Failure	454
21.4	Toxic Molecule-Induced Heart Failure 455	
21.4.1	Adriamycin-Induced Heart Failure in Rats 455	
21.4.2	Monocrotaline-Induced Right Ventricular Heart Failure 455	
21.5	Heart Failure Models Related to Myocardial Ischemia and/or	
	Myocardial Infarction 456	
21.5.1	Myocardial Ischemia and/or Myocardial Infarction 456	
21.5.2	Coronary Microembolization-Induced Heart Failure 457	
21.6	Pacing-Induced Heart Failure 458	
21.7	Gene Mutation-Induced Cardiomyopathies 460	
21.7.1	Cardiomyopathic Hamsters 460	
21.7.2	Golden Retriever Muscular Dystrophy Dogs 460	
21.7.3	Genetic Modification-Induced Cardiomyopathies in Mice 461	
21.8	Translation to Clinics: Limitations and Difficulties 462	
	References 462	
22	Endocrine Disorders 473	
	Thomas Cuny, Anne Barlier, and Alain Enjalbert	
22.1	Introduction 473	
22.2	Animal Models in Autoimmune Endocrine Diseases 474	
22.2.1	Animal Models of Autoimmune Thyroiditis 474	
22.2.2	Animal Models for Addison's Disease 476	
22.2.3	Animal Models for Other Endocrine Autoimmune Diseases 476	
22.3	Animal Models in Endocrine Tumors 477	
22.3.1	Multiple Endocrine Neoplasia Syndromes 477	
22.3.2	Adrenal Tumorigenesis 478	
22.3.3	Thyroid Tumorigenesis 481	
22.3.4	Pituitary Tumorigenesis 482	
22.4	Animal Models in Endocrine Physiology: Organogenesis,	
	Reproduction, and Metabolism 485	
22.4.1	Pituitary Development Disorders: Lessons from	
	Animal Models 485	
22.4.2	Animal Models and Reproductive Function 487	
22.4.3	Animal Models Used in Calcium Homeostasis Studies 489	
22.5	Translation to Clinics: Limitations and Difficulties 490	
	References 491	
23	Gastrointestinal Disorders: A Patho-biotechnology Approach to Probiotic Therapy 497 Roy D. Sleator	
23.1	Introduction 497	
23.2	Delivery: Improving Probiotic Resistance to Process-Induced St	resses
23.3	and Storage Conditions 498 Survival: Improving Probiotic–Host Colonization 500	
23.3	Survival improving Frobiotic=Frost Colonization 500	

XVI Contents

23.4	Efficacy: "Designer Probiotics" 500
23.5	Translation to Clinics: Limitations and Difficulties 501
	Acknowledgment 502
	References 502
24	Renal Disorders 505
	Dominique Guerrot, Christos Chatziantoniou, and Jean-Claude Dussaule
24.1	Introduction 505
24.2	Animal Models 506
24.2.1	The RenTg Model of CKD 507
24.2.1.1	Benefits of the RenTg Model 509
24.2.2	Unilateral Ureteral Obstruction 510
24.2.2.1	Technical Aspects 510
24.2.2.2	Pathology and Pathophysiology 511
24.2.2.3	Clinical Relevance and Limits 511
24.2.3	Renal Ischemia–Reperfusion 511
24.2.3.1	Technical Aspects 512
24.2.3.2	Pathology and Pathophysiology 512
24.2.3.3	Clinical Relevance and Limits 513
24.2.4	Experimental Alloimmune Glomerulonephritis 513
24.2.4.1	Technical Aspects 513
24.2.4.2	Pathology and Pathophysiology 514
24.2.4.3	Clinical Relevance and Limits 514
24.2.5	Angiotensin II-Mediated Hypertensive Nephropathy 514
24.2.5.1	Technical Aspects 515
24.2.5.2	Pathology and Pathophysiology 515
24.2.5.3	Clinical Relevance and Limits 516
24.2.6	I-NAME-Mediated Hypertensive Nephropathy 516
24.2.6.1	Technical Aspects 516
24.2.6.2	Pathology and Pathophysiology 516
24.2.6.3	Clinical Relevance and Limits 517
24.3	Translation to Clinics: Limitations and Difficulties 518
	References 518
25	Genitourinary Disorders: Lower Urinary Tract and
	Sexual Functions 523
	Pierre Clément, Delphine Behr-Roussel, and François Giuliano
25.1	Introduction 523
25.2	Lower Urinary Tract Function 523
25.2.1	Physiology of Micturition 524
25.2.2	Investigation of Lower Urinary Tract Function 524
25.2.2.1	Cystometry Evaluation 524
25.2.2.2	Evaluation of Urethral Function 525
25.2.2.3	Bladder Afferent Recording 526
25.2.3	Pathophysiological Models 527

- 25.2.3.1 Bladder Outlet Obstruction 527
- 25.2.3.2 Overactive Bladder 527
- 25.2.3.3 Neurogenic Detrusor Overactivity 528
- 25.2.3.4 Painful Bladder Syndrome/Interstitial Cystitis 528
- 25.3 Sexual Functions 529
- 25.3.1 Physiology of Female and Male Sexual Response 529
- 25.3.2 Models for Sexual Behavior 530
- 25.3.2.1 Sexual Preference Paradigms 530
- 25.3.2.2 Copulatory Tests 531
- 25.3.3 Investigation of the Peripheral Female Sexual Response 532
- 25.3.4 Investigation of Erection 532
- 25.3.4.1 Penile Reflex 532
- 25.3.4.2 Erection in Conscious Animals 533
- 25.3.4.3 Intracavernosal Pressure Measurement 533
- 25.3.4.4 Pharmacologically Induced Erection 534
- 25.3.4.5 Neurally Evoked Erection 534
- 25.3.5 Investigation of Ejaculation 534
- 25.3.5.1 Physiological Markers of Emission and Expulsion Phases 534
- 25.3.5.2 Pharmacologically Induced Ejaculation 535
- 25.3.5.3 Lumbar Spinothalamic Neurons Electrical Stimulation 535
- 25.3.5.4 Expulsion Spinal Reflex 535
- 25.3.6 Pathophysiological Models 536
- 25.3.6.1 Female Sexual Dysfunctions 536
- 25.3.6.2 Erectile Dysfunction 536
- 25.3.6.3 Ejaculatory Disorders 538
- 25.4 Translation to Clinics: Difficulties and Limitations 538 References 540

Index 543