

Contents

Advisory Board Members *xi*

Preface *xiii*

Part I General Aspects 1

1	Trends in Peptide Therapeutics	3
	<i>Florence M. Brunel, Fa Liu, and John P. Mayer</i>	
1.1	Introduction	3
1.2	Peptides in Metabolic Diseases	4
1.2.1	Insulins	4
1.2.2	Glucagon-like Peptide-1	6
1.2.3	Glucagon	8
1.2.4	Combination Therapies	8
1.3	Peptide Antibiotics	9
1.3.1	Non-ribosomally Synthesized	9
1.3.2	Ribosomally Synthesized	11
1.4	Peptides in Cancer	12
1.4.1	Luteinizing Hormone Releasing Hormone	12
1.4.2	Somatostatin	13
1.4.3	Peptide–Drug Conjugates	14
1.4.4	Cancer Vaccines	15
1.5	Peptides in Bone Diseases	16
1.5.1	Calcitonin	16
1.5.2	Parathyroid Hormone (PTH) (1–34) and (1–84)	17
1.5.3	Parathyroid Hormone Related Protein	18
1.5.4	Incretin Peptides	19
1.5.5	Bone Morphogenic Protein-Derived Peptides	19
1.6	Peptides in Gastrointestinal Diseases	19
1.6.1	Glucagon-like Peptide-2	19
1.6.2	Guanylate Cyclase-C Agonists	20
1.7	Emerging Trends in Peptide Drug Discovery	22
1.7.1	Cell-Penetrating Peptides	22
1.7.2	Macrocyclic Peptides	23
1.8	Summary	23

Acknowledgment	24
List of Abbreviations	24
References	25
Biographies	34
2	Physicochemical Parameters of Recently Approved Oral Drugs 35
<i>Andreas Ritzén and Laurent David</i>	
2.1	Introduction 35
2.2	FDA-Approved Drugs 2007–2017 36
2.2.1	Conclusions 40
2.3	Polar Surface Area in bRo5 Territory 42
2.3.1	Finding Chameleons with Molecular Dynamics 44
2.3.2	Conclusions 48
2.3.3	Methods 49
	List of Abbreviations 50
	References 51
	Biographies 52
Part II Drug Class Studies 55	
3	Antibody–Drug Conjugates: Empowering Antibodies for the Fight Against Cancer 57
<i>Caroline Denevault-Sabourin, Francesca Bryden, Marie-Claude Viaud-Massuard, and Nicolas Joubert</i>	
3.1	Introduction 57
3.2	First Generation ADCs 58
3.2.1	Molecular Design 58
3.2.2	Mechanism of Action 60
3.2.3	Therapeutic Applications 60
3.2.4	Adverse Effects 60
3.3	Second Generation ADCs 62
3.3.1	Molecular Design 62
3.3.2	Mechanism of Action 63
3.3.3	Therapeutic Applications 67
3.3.4	Adverse Effects 67
3.4	Toward Next Generation ADCs 68
3.4.1	Site-Specific ADCs 69
3.4.2	New Formats of Immunoconjugates 70
3.4.3	ADC with New Payloads 74
3.5	Summary 76
	List of Abbreviations 76
	References 77
	Biographies 81

4	Dopamine D₂ Partial Agonists – Discovery, Evolution, and Therapeutic Potential	83
	<i>Marlene Jacobson, Wayne Childers, and Magid Abou-Gharbia</i>	
4.1	Introduction	83
4.2	Dopamine and Dopamine Receptors	83
4.2.1	Functional Selectivity and Biased Ligand Signaling	86
4.3	Schizophrenia and Earlier Antipsychotic Agents	86
4.4	Dopamine Partial Agonism	88
4.5	D ₂ Partial Agonists	89
4.5.1	Dopamine-like Scaffolds – The “Classical” Pharmacophore	89
4.5.2	Non-dopamine-like Scaffolds – The “Nonclassical” Pharmacophore	91
4.5.3	Compounds Related to Bifeprunox	92
4.5.4	Methylaminochroman Scaffold – Aplindore	94
4.5.5	D ₂ Partial Agonist Drug Discovery in the Wake of the Marketed Drugs	95
4.5.5.1	D ₂ Partial Agonists Discovered Using Traditional D ₂ Functional Screening	96
4.5.5.2	Bivalent Ligands	98
4.5.5.3	β-Arrestin-Biased D ₂ Partial Agonists	98
4.5.5.4	G-protein-Biased D ₂ Partial Agonists	99
4.5.6	Arylpiperazines and the Discovery of Aripiprazole and Brexpiprazole	101
4.5.7	The Road Leading to Cariprazine	102
4.6	Marketed D ₂ Partial Agonist Antipsychotics	103
4.6.1	Aripiprazole (Abilify [®])	104
4.6.1.1	History	105
4.6.1.2	Synthesis	105
4.6.1.3	Drug Substance	105
4.6.1.4	Pharmacology	105
4.6.1.5	Functional Selectivity and Biased Ligand Signaling	107
4.6.1.6	Pharmacokinetics and Metabolism	107
4.6.1.7	Clinical Data	107
4.6.2	Brexpiprazole (Rexulti [®])	108
4.6.2.1	History	108
4.6.2.2	Synthesis	108
4.6.2.3	Drug Substance	109
4.6.2.4	Pharmacology	109
4.6.2.5	Functional Selectivity and Biased Ligand Signaling	110
4.6.2.6	Pharmacokinetics and Metabolism	110
4.6.2.7	Clinical Data	110
4.6.3	Cariprazine (Vraylar [®])	111
4.6.3.1	History	111
4.6.3.2	Synthesis	112

4.6.3.3	Drug Substance	112
4.6.3.4	Pharmacology	112
4.6.3.5	Functional Selectivity and Biased Ligand Signaling	113
4.6.3.6	Pharmacokinetics	113
4.6.3.7	Clinical Data	114
4.7	Conclusions	115
	List of Abbreviations	116
	References	117
	Biographies	129

Part III Case Studies 131

5	Discovery of Etelcalcetide for the Treatment of Secondary Hyperparathyroidism in Patients with Chronic Kidney Disease	133
	<i>Amos Baruch and Derek Maclean</i>	
5.1	Introduction	133
5.2	Compound Design and Structure–Activity Relationships	135
5.2.1	Optimization of the Cationic Charge	135
5.2.2	Alanine Scan of dCR ₆	136
5.2.3	Double Alanine Scan of dCR ₆	138
5.2.4	SAR of Alanine Residues in Ac-carrar-NH ₂ and Ac-crrar-NH ₂	138
5.2.5	Importance of the Thiol Residue	140
5.2.6	Thiol Conjugates – Selection of Etelcalcetide	140
5.3	Preclinical Studies	141
5.4	Mechanism of Action of Etelcalcetide	144
5.5	Clinical Studies	145
5.6	Summary	149
	Acknowledgments	149
	List of Abbreviations	149
	References	150
	Biographies	153
6	Development of Lenvatinib Mesylate, an Angiogenesis Inhibitor Targeting VEGF and FGF Receptors	155
	<i>Akihiko Tsuruoka, Yasuhiro Funahashi, Junji Matsui, and Tomohiro Matsushima</i>	
6.1	Introduction	155
6.2	Recent Progress in the Development of Molecular Targeted Anticancer Agents	155
6.3	Tumor Angiogenesis	156
6.4	Development of Resistance to VEGF-Targeting Drugs	156
6.5	Discovery of Lenvatinib, a Drug Targeting VEGFR and FGFR	157
6.6	Inhibition of Kinase Activity by Lenvatinib and Discovery of the Novel Type V Kinase-Binding Mode	158

6.7	Antitumor Effects of Lenvatinib in Human Thyroid Cancer Cell Lines	161
6.8	Antitumor Effects of Lenvatinib in Human Renal Cell Cancer Cell Lines and Its Mechanism of Action	162
6.9	Conclusions and Perspectives	162
	List of Abbreviations	163
	References	164
	Biographies	167
7	Ocrelizumab: A New Generation of anti CD20 mAb for Treatment of Multiple Sclerosis	169
	<i>Andrew C. Chan, Paul Brunetta, and Peter Chin</i>	
7.1	Introduction: B Cells Play Critical Roles in Immunity	169
7.2	Role of B Cells in Autoimmunity	172
7.3	CD20-Targeting Therapeutic Antibodies	173
7.4	Rituximab: the First Anti-CD20 mAb Experience in Autoimmunity	176
7.5	Effects of Rituximab on Antibodies and Autoantibodies	178
7.6	Rituximab in AAV and Other Autoimmune Disorders	178
7.7	Beginnings of Ocrelizumab	179
7.8	Multiple Sclerosis	180
7.9	Multiple Sclerosis Disease Pathogenesis	181
7.10	Rituximab: The First Anti-CD20 mAb Experience in Multiple Sclerosis	183
7.10.1	HERMES Junior	183
7.10.2	HERMES	183
7.10.3	OLYMPUS	184
7.11	Ocrelizumab in Multiple Sclerosis	184
7.11.1	OPERA	185
7.11.2	ORATORIO	186
7.12	The Conundrum of B Cells in Multiple Sclerosis	187
7.13	Final Comments	187
	List of Abbreviations	188
	Acknowledgments	189
	References	189
	Biographies	198
8	The Story of Rucaparib (Rubraca)	201
	<i>Bernard T. Golding</i>	
8.1	Introduction	201
8.2	Benzoxazole-/Benzimidazole-carboxamides and Quinazolinones	205
8.3	The Road to Rucaparib/Rubraca	212
8.4	The Emergence of Single-Agent Therapy	216
8.5	Clinical Studies	217

8.6	Conclusion	218
	Acknowledgments	218
	References	219
	Biography	223
9	Discovery and Development of Venetoclax, a Selective Antagonist of BCL 2	225
	<i>Wayne J. Fairbrother, Joel D. Levenson, Deepak Sampath, and Andrew J. Souers</i>	
9.1	Introduction	225
9.2	Discovery of Venetoclax – Structure-Based Design	227
9.3	Preclinical Studies	232
9.3.1	Mechanism of Action	232
9.3.2	Predictive Biomarkers of Venetoclax Sensitivity	233
9.3.3	Efficacy of Venetoclax as Monotherapy and in Combination with Targeted Agents or Chemotherapeutics	234
9.4	Clinical Studies	236
	List of Abbreviations	238
	References	239
	Biographies	244
	Index	247