Contents

List of Contributors XV Preface XXI A Personal Foreword XXIII

Part One Fundamentals of Chemokines and Chemokine Receptors 1

v

1	Structural Aspects of Chemokines and their Interactions with Receptors and Glycosaminoglycans 3 Amanda E. I. Proudfoot, India Severin, Damon Hamel, and Tracy M. Handel
1 1	Introduction 3
1.1	Receptor_Ligand Interactions 5
1.2	Ligand Structure 8
131	Tertiary and Quaternary Structures 8
132	Functional Role of Tertiary and Quaternary Structures 12
133	Hetero-Oligomerization 13
1.5.5	Receptor Structure 13
141	Modifications to the N-Termini of Chemokines and their
1	Effect on Receptor Activation 16
1.5	Glycosaminoglycan Binding Sites 17
1.6	Chemokine Analogs– Research Tools and Potential Therapeutics? 20
	References 23
2	Structural Insights for Homology Modeling of Chemokine Receptors 33
	Leonardo Pardo, Xavier Deupi, Arnau Cordomí, Cedric Govaerts,
	and Mercedes Campillo
2.1	Introduction 33
2.2	Chemokines 35
2.3	The Transmembrane Domain of Chemokine Receptors 36
2.3.1	Transmembrane Helix 1 37
2.3.2	Transmembrane Helix 2 37

Chemokine Receptors as Drug Targets. Edited by Martine J. Smit, Sergio A. Lira, and Rob Leurs Copyright © 2011 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim ISBN: 978-3-527-32118-6

- Contents
 - 2.3.3 Transmembrane Helix 3 38
 - 2.3.4 Transmembrane Helix 4 38
 - 2.3.5 Transmembrane Helix 5 39
 - 2.3.6 Transmembrane Helix 6 39
 - 2.3.7 Transmembrane Helix 7 39
 - Structural and Functional Role of Internal Water Molecules 2.4 40
 - The Structure of the Extracellular Domain of Chemokine Receptors 2.5 41
 - 2.6 The Structure of the Intracellular Domain 41
 - 2.7 The Binding of Chemokines to Chemokine Receptors 41
 - The Binding of Small-Molecule Ligands to Chemokine Receptors 42 2.8
 - Molecular Processes of Receptor Activation 42 2.9
 - The Binding of the G Protein 44 2.10
 - 2.11 Receptor Oligomerization 45
 - 2.12 Conclusions 45
 - References 45
 - 3 Signaling Events Involved in Chemokine-Directed T Lymphocyte Migration 51
 - Stephen G. Ward
 - The Role of GTPases in Chemokine-Directed Lymphocyte 3.1 Migration 51
 - 3.2 Class 1 PI3Ks and their Role in Cell Migration: An Overview 52
 - 3.3 Do PI3K-Dependent Signals Contribute to T Lymphocyte Migration in Response to Chemokines? 53
 - 3.4 Role of PI3K in T Lymphocyte Homing and Migration In Vivo 54
 - Role of PI3K in Interstitial T Lymphocyte Motility 55 3.5
 - Role of Phospholipase C and Protein Kinase C Signaling 3.6 in Chemokine-Directed T Lymphocyte Migration 56
 - 3.7 Concluding Remarks and Future Directions 57 References 59
 - 4 The Atypical Chemokine Receptors 67
 - Mark D. Singh, Robert J. B. Nibbs, and Gerard J. Graham
 - 4.1 D6, an Atypical Receptor for Pro-Inflammatory CC Chemokines 67
 - 4.1.1 D6 Scavenges Chemokines In Vitro 68
 - 4.1.2 D6 Expression In Vivo 69
 - 4.1.3 Explorations of D6 Function In Vivo 70
 - 4.2 CCX-CKR, an Atypical Receptor for Homeostatic CC Chemokines 73
 - CXCR7: A Second Receptor for CXCL11 and CXCL12 with Critical 4.3
 - Roles in Development and Tumorigenesis 75
 - 4.3.1 CXCR7 in Development 75
 - CXCR7 in Cancer 76 4.3.2
 - DARC: A Promiscuous Pro-Inflammatory Atypical Chemokine Receptor 4.4 on Red Blood Cells and Endothelial Cells 77
 - 4.4.1 Function of Chemokine Binding to DARC 77

- 4.4.2 DARC Interacts with Non-Chemokine Proteins 78
- 4.4.3 What Can DARC Negative People Tell Us About DARC Function? 79
- 4.5 Summary 79 References 79
- 5 Targeting Chemokine Receptor Dimers: Are there Two (or More) to Tango? 85

Henry F. Vischer, Saskia Nijmeijer, and Marc Parmentier

- 5.1 Introduction 85
- 5.2 Chemokines and their Receptors 85
- 5.3 GPCRs Exist and Function as Dimers 86
- 5.4 Detection of GPCR Dimerization 87
- 5.5 Chemokine Receptor Dimerization 90
- 5.6 Constitutive Versus Induced Chemokine Receptor Dimerization 93
- 5.7 Functional Consequences of Chemokine Receptor Dimerization 95
- 5.8 (Patho-)Physiological Consequences of Chemokine Receptor Dimerization 95
- 5.8.1 Chemokine Receptor Heterodimerization with Chemokine Receptors 96
- 5.8.2 Chemokine Receptor Heterodimerization with Decoy Chemokine Receptor 96
- 5.8.3 Chemokine Receptor Heterodimerization with Virally Encoded GPCRs 96
- 5.8.4 Chemokine Receptor Heterodimerization with Opioid Receptors 97
- 5.8.5 Chemokine Receptor Heterodimers: Innovative Drug Targets? 97 References 98
- Part Two Chemokine Receptors in Disease 105

6	Chemokine Receptors in Inflammatory	/ Diseases	107

- Aletta D. Kraneveld, Saskia Braber, Saskia Overbeek, Petra de Kruijf, Pim Koelink, and Martine J. Smit
- 6.1 Introduction 107
- 6.2 Chemokine Receptors on Inflammatory/Immune Cells 108
- 6.2.1 Chemokine Receptors and Innate Immune Cells 108
- 6.2.1.1 Monocytes and Macrophages 108
- 6.2.1.2 Dendritic Cells 109
- 6.2.1.3 Neutrophils 109
- 6.2.1.4 Eosinophils 110
- 6.2.1.5 Basophils 110
- 6.2.1.6 Mast Cells 111
- 6.2.1.7 Natural Killer Cells 111
- 6.2.2 Chemokine Receptors and Adaptive Immune Cells 112
- 6.2.2.1 B Lymphocytes 112
- 6.2.2.2 T Lymphocytes 113

VIII Contents

6.2.3	Conclusion 114
6.3	Chemokine Receptors and Inflammatory Lung Diseases 114
6.3.1	COPD 116
6.3.2	Chemokine Receptors in COPD 116
6.3.3	Asthma 118
6.3.4	Chemokine Targets in Asthma 119
6.4	Chemokine and Inflammatory Bowel Diseases 121
6.4.1	Inflammatory Bowel Disease 121
6.4.2	Chemokine Receptors in Inflammatory Bowel Disease 122
6.4.3	Chemokine-Mediated Neuronal Activation in Inflammatory
	Bowel Disease 124
6.5	Chemokine Receptors and Rheumatoid Arthritis 125
6.5.1	Rheumatoid Arthritis 125
6.5.2	Chemokine Receptors and Their Ligands in Rheumatoid Arthritis 126
6.6	Chemokine Receptors and Atherosclerosis 128
6.6.1	Atherosclerosis 128
6.6.2	Chemokine and their Receptors in Atherosclerosis 129
6.7	Chemokine Receptors in Multiple Sclerosis 131
6.7.1	Multiple Sclerosis 132
6.7.2	Chemokines and their Receptors in Multiple Sclerosis 132
6.8	Chemokine Receptors and Psoriasis 134
6.8.1	Psoriasis 134
6.8.2	Chemokines and their Receptors in Psoriasis 135
6.9	Concluding Remarks 136
	References 137
7	Chemokines and their Receptors in Central Nervous
	System Disease 151
	Knut Biber and Hendrikus W. G. M. Boddeke
7.1	Introduction 151
7.2	Families of Chemokines 151
7.3	Chemokine Pharmacology 152
7.4	Chemokines and Chemokine Receptors: A Complex System 152
7.4.1	Expression of Chemokines and their Receptors in the CNS 153
7.4.2	Involvement of Chemokines in Blood–Brain Barrier Disruption
	Associated with Neurodegenerative Disease 153
7.5	The Role of the Chemokinergic System in Multiple Sclerosis
	and Experimental Autoimmune Encephalitis 154
7.5.1	Chemokines: Attractors for Blood Lymphocytes in MS and EAE? 154
7.6	The Role of Chemokines in Brain Ischemia 155
7.6.1	Functional Involvement of Chemokines in Ischemic
	Neurodegeneration 156
7.7	Chemokines in HIV-Associated Dementia 157
7.7.1	Involvement of Chemokine Receptors in HIV Infection

Contents IX

7.7.2	Involvement of CXCR4 in gp120-Induced Neurotoxicity 157
7.7.3	The Role of CX3CL1 in HAD 158
7.8	Chemokines in Neuropathic Pain 159
7.9	Conclusions 160
	References 160
8	Chemokines and Cancer Metastasis 167
	Amanda Burkhardt and Albert Zlotnik
8.1	Introduction 167
8.2	CXCR4 and CCR7 Receptors Play Special Roles in Cancer
	Metastasis 168
8.3	Retrospective Clinical Data Supports a Role for Chemokines
0 1	In Cancer Metastasis 169
0.4	of Metastatic Lesions? 170
8.5	CXCR4 is a Key Player in the Development of Zebrafish;
	Role of CXCR7 170
8.6	The CXCR4/CXCL12 Axis in Stem Cell Homing in the Bone
	Marrow 172
8.7	Conclusions and Future Directions 172
	References 173
9	Constitutively Active Viral Chemokine Receptors: Tools for Immune
9	Constitutively Active Viral Chemokine Receptors: Tools for Immune Subversion and Pathogenesis 177
9	Constitutively Active Viral Chemokine Receptors: Tools for Immune Subversion and Pathogenesis 177 David Maussang, Gerold Bongers, Sergio A. Lira, and Martine J. Smit
9 9.1	Constitutively Active Viral Chemokine Receptors: Tools for Immune Subversion and Pathogenesis 177 David Maussang, Gerold Bongers, Sergio A. Lira, and Martine J. Smit Introduction 177
9 9.1 9.2	Constitutively Active Viral Chemokine Receptors: Tools for Immune Subversion and Pathogenesis 177 David Maussang, Gerold Bongers, Sergio A. Lira, and Martine J. Smit Introduction 177 Herpesviruses and Viral Diseases 180
9 9.1 9.2 9.2.1	Constitutively Active Viral Chemokine Receptors: Tools for Immune Subversion and Pathogenesis 177 David Maussang, Gerold Bongers, Sergio A. Lira, and Martine J. Smit Introduction 177 Herpesviruses and Viral Diseases 180 The Betaherpesviridae Subfamily 180
9 9.1 9.2 9.2.1 9.2.1.1	Constitutively Active Viral Chemokine Receptors: Tools for Immune Subversion and Pathogenesis 177 David Maussang, Gerold Bongers, Sergio A. Lira, and Martine J. Smit Introduction 177 Herpesviruses and Viral Diseases 180 The Betaherpesviridae Subfamily 180 The Cytomegalovirus Genus: HHV-5/HCMV 180
 9.1 9.2 9.2.1 9.2.1.1 9.2.1.2 	Constitutively Active Viral Chemokine Receptors: Tools for Immune Subversion and Pathogenesis 177 David Maussang, Gerold Bongers, Sergio A. Lira, and Martine J. Smit Introduction 177 Herpesviruses and Viral Diseases 180 The Betaherpesviridae Subfamily 180 The Cytomegalovirus Genus: HHV-5/HCMV 180 The Rhesolovirus Genus: HHV-6 and HHV-7 183
 9.1 9.2 9.2.1 9.2.1.1 9.2.1.2 9.2.2 	Constitutively Active Viral Chemokine Receptors: Tools for Immune Subversion and Pathogenesis 177 David Maussang, Gerold Bongers, Sergio A. Lira, and Martine J. Smit Introduction 177 Herpesviruses and Viral Diseases 180 The Betaherpesviridae Subfamily 180 The Cytomegalovirus Genus: HHV-5/HCMV 180 The Rhesolovirus Genus: HHV-6 and HHV-7 183 The Gammaherpesviridae Subfamily 183
 9.1 9.2 9.2.1 9.2.1.1 9.2.1.2 9.2.2 9.2.2.1 	Constitutively Active Viral Chemokine Receptors: Tools for Immune Subversion and Pathogenesis 177 David Maussang, Gerold Bongers, Sergio A. Lira, and Martine J. Smit Introduction 177 Herpesviruses and Viral Diseases 180 The Betaherpesviridae Subfamily 180 The Cytomegalovirus Genus: HHV-5/HCMV 180 The Rhesolovirus Genus: HHV-6 and HHV-7 183 The Gammaherpesviridae Subfamily 183 The Lymphocryptovirus Genus: HHV-4/EBV 183
 9.1 9.2 9.2.1 9.2.1.1 9.2.1.2 9.2.2 9.2.2.1 9.2.2.1 9.2.2.2 	Constitutively Active Viral Chemokine Receptors: Tools for Immune Subversion and Pathogenesis 177 David Maussang, Gerold Bongers, Sergio A. Lira, and Martine J. Smit Introduction 177 Herpesviruses and Viral Diseases 180 The Betaherpesviridae Subfamily 180 The Cytomegalovirus Genus: HHV-5/HCMV 180 The Rhesolovirus Genus: HHV-6 and HHV-7 183 The Gammaherpesviridae Subfamily 183 The Lymphocryptovirus Genus: HHV-4/EBV 183 The Rhadinovirus Genus: HHV-8/KSHV 183
 9.1 9.2 9.2.1 9.2.1.1 9.2.1.2 9.2.2 9.2.2.1 9.2.2.2 9.3 	Constitutively Active Viral Chemokine Receptors: Tools for Immune Subversion and Pathogenesis 177 David Maussang, Gerold Bongers, Sergio A. Lira, and Martine J. Smit Introduction 177 Herpesviruses and Viral Diseases 180 The Betaherpesviridae Subfamily 180 The Cytomegalovirus Genus: HHV-5/HCMV 180 The Rhesolovirus Genus: HHV-6 and HHV-7 183 The Gammaherpesviridae Subfamily 183 The Lymphocryptovirus Genus: HHV-4/EBV 183 The Rhadinovirus Genus: HHV-8/KSHV 183 Herpesviruses Encode Constitutively Active Viral Chemokine
 9.1 9.2 9.2.1 9.2.1.1 9.2.1.2 9.2.2 9.2.2.1 9.2.2.2 9.3 	Constitutively Active Viral Chemokine Receptors: Tools for Immune Subversion and Pathogenesis 177 David Maussang, Gerold Bongers, Sergio A. Lira, and Martine J. Smit Introduction 177 Herpesviruses and Viral Diseases 180 The Betaherpesviridae Subfamily 180 The Cytomegalovirus Genus: HHV-5/HCMV 180 The Rhesolovirus Genus: HHV-6 and HHV-7 183 The Gammaherpesviridae Subfamily 183 The Lymphocryptovirus Genus: HHV-4/EBV 183 The Rhadinovirus Genus: HHV-8/KSHV 183 Herpesviruses Encode Constitutively Active Viral Chemokine Receptors 184
 9.1 9.2 9.2.1 9.2.1.1 9.2.1.2 9.2.2 9.2.2.1 9.2.2.2 9.3 9.3.1 	Constitutively Active Viral Chemokine Receptors: Tools for Immune Subversion and Pathogenesis 177 David Maussang, Gerold Bongers, Sergio A. Lira, and Martine J. Smit Introduction 177 Herpesviruses and Viral Diseases 180 The Betaherpesviridae Subfamily 180 The Cytomegalovirus Genus: HHV-5/HCMV 180 The Rhesolovirus Genus: HHV-6 and HHV-7 183 The Gammaherpesviridae Subfamily 183 The Lymphocryptovirus Genus: HHV-4/EBV 183 The Lymphocryptovirus Genus: HHV-8/KSHV 183 Herpesviruses Encode Constitutively Active Viral Chemokine Receptors 184 Human Cytomegalovirus Encodes Four Different Viral G
 9.1 9.2 9.2.1 9.2.1.1 9.2.1.2 9.2.2 9.2.2.1 9.2.2.2 9.3 9.3.1 	Constitutively Active Viral Chemokine Receptors: Tools for Immune Subversion and Pathogenesis 177 David Maussang, Gerold Bongers, Sergio A. Lira, and Martine J. Smit Introduction 177 Herpesviruses and Viral Diseases 180 The Betaherpesviridae Subfamily 180 The Cytomegalovirus Genus: HHV-5/HCMV 180 The Rhesolovirus Genus: HHV-6 and HHV-7 183 The Gammaherpesviridae Subfamily 183 The Lymphocryptovirus Genus: HHV-4/EBV 183 The Lymphocryptovirus Genus: HHV-8/KSHV 183 Herpesviruses Encode Constitutively Active Viral Chemokine Receptors 184 Human Cytomegalovirus Encodes Four Different Viral G Protein-Coupled Receptors 184
 9.1 9.2 9.2.1 9.2.1.1 9.2.1.2 9.2.2 9.2.2.1 9.2.2.2 9.3 9.3.1 9.3.1.1 	Constitutively Active Viral Chemokine Receptors: Tools for Immune Subversion and Pathogenesis 177 David Maussang, Gerold Bongers, Sergio A. Lira, and Martine J. Smit Introduction 177 Herpesviruses and Viral Diseases 180 The Betaherpesviridae Subfamily 180 The Cytomegalovirus Genus: HHV-5/HCMV 180 The Cytomegalovirus Genus: HHV-6 and HHV-7 183 The Gammaherpesviridae Subfamily 183 The Lymphocryptovirus Genus: HHV-4/EBV 183 The Lymphocryptovirus Genus: HHV-8/KSHV 183 Herpesviruses Encode Constitutively Active Viral Chemokine Receptors 184 Human Cytomegalovirus Encodes Four Different Viral G Protein-Coupled Receptors 184 The Chemokine Receptor US28 Mediates HCMV-Induced
 9.1 9.2 9.2.1 9.2.1.2 9.2.2 9.2.2.1 9.2.2.2 9.3.1 9.3.1.1 9.3.1.1 	Constitutively Active Viral Chemokine Receptors: Tools for Immune Subversion and Pathogenesis 177 David Maussang, Gerold Bongers, Sergio A. Lira, and Martine J. Smit Introduction 177 Herpesviruses and Viral Diseases 180 The Betaherpesviridae Subfamily 180 The Cytomegalovirus Genus: HHV-5/HCMV 180 The Rhesolovirus Genus: HHV-6 and HHV-7 183 The Gammaherpesviridae Subfamily 183 The Lymphocryptovirus Genus: HHV-4/EBV 183 The Lymphocryptovirus Genus: HHV-8/KSHV 183 Herpesviruses Encode Constitutively Active Viral Chemokine Receptors 184 Human Cytomegalovirus Encodes Four Different Viral G Protein-Coupled Receptors 184 The Chemokine Receptor US28 Mediates HCMV-Induced (Patho)Physiological Effects 184
 9.1 9.2 9.2.1 9.2.1.1 9.2.1.2 9.2.2 9.2.2 9.2.2.1 9.2.2.2 9.3 9.3.1 9.3.1.1 9.3.1.2 	Constitutively Active Viral Chemokine Receptors: Tools for Immune Subversion and Pathogenesis 177 David Maussang, Gerold Bongers, Sergio A. Lira, and Martine J. Smit Introduction 177 Herpesviruses and Viral Diseases 180 The Betaherpesviridae Subfamily 180 The Cytomegalovirus Genus: HHV-5/HCMV 180 The Rhesolovirus Genus: HHV-6 and HHV-7 183 The Gammaherpesviridae Subfamily 183 The Lymphocryptovirus Genus: HHV-4/EBV 183 The Rhadinovirus Genus: HHV-8/KSHV 183 Herpesviruses Encode Constitutively Active Viral Chemokine Receptors 184 Human Cytomegalovirus Encodes Four Different Viral G Protein-Coupled Receptors 184 The Chemokine Receptor US28 Mediates HCMV-Induced (Patho)Physiological Effects 184 The Constitutively Active Orphan Chemokine Receptor
 9.1 9.2 9.2.1 9.2.1.1 9.2.1.2 9.2.2 9.2.2.1 9.2.2.2 9.3 9.3.1 9.3.1.1 9.3.1.2 9.3.1.3 	Constitutively Active Viral Chemokine Receptors: Tools for Immune Subversion and Pathogenesis 177 David Maussang, Gerold Bongers, Sergio A. Lira, and Martine J. Smit Introduction 177 Herpesviruses and Viral Diseases 180 The Betaherpesviridae Subfamily 180 The Cytomegalovirus Genus: HHV-5/HCMV 180 The Rhesolovirus Genus: HHV-6 and HHV-7 183 The Gammaherpesviridae Subfamily 183 The Lymphocryptovirus Genus: HHV-4/EBV 183 The Rhadinovirus Genus: HHV-8/KSHV 183 Herpesviruses Encode Constitutively Active Viral Chemokine Receptors 184 Human Cytomegalovirus Encodes Four Different Viral G Protein-Coupled Receptors 184 The Chemokine Receptor US28 Mediates HCMV-Induced (Patho)Physiological Effects 184 The Constitutively Active Orphan Chemokine Receptor UL33 188
 9.1 9.2 9.2.1 9.2.1.1 9.2.1.2 9.2.2 9.2.2.1 9.2.2.2 9.3 9.3.1 9.3.1.1 9.3.1.2 9.3.1.3 	Constitutively Active Viral Chemokine Receptors: Tools for Immune Subversion and Pathogenesis 177 David Maussang, Gerold Bongers, Sergio A. Lira, and Martine J. Smit Introduction 177 Herpesviruses and Viral Diseases 180 The Betaherpesviridae Subfamily 180 The Cytomegalovirus Genus: HHV-5/HCMV 180 The Rhesolovirus Genus: HHV-6 and HHV-7 183 The Gammaherpesviridae Subfamily 183 The Lymphocryptovirus Genus: HHV-4/EBV 183 The Rhadinovirus Genus: HHV-8/KSHV 183 Herpesviruses Encode Constitutively Active Viral Chemokine Receptors 184 Human Cytomegalovirus Encodes Four Different Viral G Protein-Coupled Receptors 184 The Chemokine Receptor US28 Mediates HCMV-Induced (Patho)Physiological Effects 184 The Constitutively Active Orphan Chemokine Receptor UL33 188 The Chemokine Receptor-Related US27 and UL78 Orphan Recentors 188
 9.1 9.2 9.2.1 9.2.1.2 9.2.2 9.2.21 9.2.2 9.3.1 9.3.1.1 9.3.1.2 9.3.1.3 9.3.2 	Constitutively Active Viral Chemokine Receptors: Tools for Immune Subversion and Pathogenesis 177 David Maussang, Gerold Bongers, Sergio A. Lira, and Martine J. Smit Introduction 177 Herpesviruses and Viral Diseases 180 The Betaherpesviridae Subfamily 180 The Cytomegalovirus Genus: HHV-5/HCMV 180 The Rhesolovirus Genus: HHV-6 and HHV-7 183 The Gammaherpesviridae Subfamily 183 The Lymphocryptovirus Genus: HHV-4/EBV 183 The Rhadinovirus Genus: HHV-8/KSHV 183 Herpesviruses Encode Constitutively Active Viral Chemokine Receptors 184 Human Cytomegalovirus Encodes Four Different Viral G Protein-Coupled Receptors 184 The Chemokine Receptor US28 Mediates HCMV-Induced (Patho)Physiological Effects 184 The Constitutively Active Orphan Chemokine Receptor UL33 188 The Chemokine Receptor-Related US27 and UL78 Orphan Receptors 188 Roseoloviruses-Encoded Chemokine Receptors: The U12 and

X Contents

9.3.3	EBV-Encoded Constitutively Active Orphan vGPCR BILF1 190
9.3.4	ORF74, the Tumorigenic Constitutively Active Chemokine Receptor Encoded by KSHV 190
9.3.4.1	ORF74 Constitutively Activates Multiple Signaling Pathways in Different Cell Types 191
9.3.4.2	ORF74 Expression Mimics KSHV-Induced Transformation 193
9.4	Concluding Remarks 194 References 196
Part Three	Targeting Chemokine Receptors 207
10	CCR5 Antagonists in HIV 209

	David C. Pryde and Christopher G. Barber
10.1	Introduction 209
10.1.1	HIV and AIDS 209
10.1.2	Viral Entry as a Therapeutic Target 210
10.1.3	CCR5 as a Therapeutic Target 211
10.1.4	Enabling Drug Discovery Programs Targeting CCR5 211
10.2	CCR5 Antagonist Programs 212
10.2.1	Merck 212
10.2.2	Novartis 214
10.2.3	Pfizer 215
10.2.4	Incyte 218
10.2.5	Schering Plough 218
10.2.6	Berlex 220
10.2.7	GlaxoSmithKline/Ono 220
10.2.8	Takeda 221
10.2.9	AstraZeneca 222
10.2.10	Recent Disclosures 222
10.2.11	Overview of Published CCR5 Antagonists 224
10.3	Molecular Interactions and Binding Modes of CCR5 Receptor
	Antagonists 225
10.4	Resistance to CCR5 Receptor Antagonists 227
10.5	Outlook 228
	References 229
11	CXCR4 as a Therapeutic Target 239
	Ken Y.C. Chow and Françoise Bachelerie
11.1	Biology and Physiological Role of CXCR4 239
11.1.1	General Introduction 239
11.1.2	Regulation of CXCR4 Expression 240
11.1.2.1	Transcriptional Regulation 240
11.1.2.2	Post-Transcriptional Regulation 241
11.1.3	Physiological Functions of the CXCR4 Receptor 242

Role in Leukocytes Trafficking and Development 242 11.1.3.1

11.1.3.2 Role in Neovascularization and Angiogenesis (Pre- and Post-Natal) 243 Role in Embryonic Development: Phenotypes of CXCL12 11.1.3.3 and CXCR4-Knockout Mice 244 11.1.3.4 Role in Embryonic Development: Insights from the Zebra Fish Model 245 Signal Transduction via the CXCR4 Receptor 246 11.1.4 11.1.4.1 Interaction with the Cognate Ligand – CXCL12 246 11.1.4.2 Activation of Heterotrimeric G Proteins 247 Regulation of CXCR4 G Protein-Dependent Signaling 247 11.1.4.3 11.1.4.4 Activation and Regulation of β-Arrestin-Dependent Signaling Pathways 248 Other Factors Affecting CXCR4 Signaling: Role of 11.1.4.5 Receptor Oligomerisation 248 11.2 Patho-Physiological Role of CXCR4: Potential as a Therapeutic Target 249 Role in HIV Infection 249 11.2.1 11.2.2 Role in Inflammatory Diseases 250 Role in Cancer Development 251 11.2.3 11.2.4 The WHIM Syndrome (WS) 252 Potential of CXCR4 as Therapeutic Target 252 11.2.5 11.2.5.1 Application in HIV-Infection 252 11.2.5.2 Application in the Development of Cancer and Stem Cell Mobilization 254 11.3 Concluding Remarks 255 References 256 12 Low Molecular Weight CXCR2 Antagonists as Promising Therapeutics 279 Katsuhiro Mihara and Jac Wijkmans Introduction 279 12.1 CXCR2 Ligands and Signal Transduction 279 12.2 12.3 Biological Functions 280 12.3.1 Leukocytes 280 12.3.2 Nonhematopoietic Cells and Cells of the Central Nervous System 281 CXCR2 in Inflammatory Disorders 282 12.4 12.4.1 Chronic Obstructive Pulmonary Disease 282 12.4.2 Asthma 282 12.4.3 Acute Lung Injury and Acute Respiratory Distress Syndrome 283 12.4.4 Atherosclerosis 283 Other Inflammatory Disorders 283 12.4.5 12.5 Low Molecular Weight CXCR2 Antagonists 284 12.5.1 2-Hydroxyphenyl Ureas 284 12.5.2 Urea Isosteres 286

XII Contents

12.5.3	Thiazolopyrimidines 289
12.5.4	Triazolethiols 290
12.5.5	2-Amino-3-Heteroaryl Quinazolines 290
12.5.6	Indolylbuteric Acid Derivatives 291
12.5.7	2-Imidazolyl Pyrimidines 291
12.5.8	Nicotinamide N-Oxides 291
12.5.9	2-Arylpropionic Acid Derivatives 292
12.5.10	Diaryl Isoxazoles 293
12.6	Challenges and Future Perspectives 293
	References 294
13	Therapeutic Targeting of the CXCR3 Receptor 301
	Maikel Wijtmans, Iwan J. P. de Esch, and Rob Leurs
13.1	The CXCR3 Receptor 301
13.2	CXCR3 as a Potential Drug Target 302
13.2.1	Use of CXCR3-KO Mice 302
13.2.2	Targeting of CXCR3 or its Endogenous Ligands by Antibodies 303
13.3	The Development of CXCR3 Antagonists 303
13.3.1	Publications on Small CXCR3 Antagonists 304
13.3.2	Patents on Small CXCR3 Antagonists 310
13.3.3	Protein-Based CXCR3 Antagonists 312
13.4	CXCR3 Antagonists in Disease Models and in the Clinic 312
135	Conclusion and Outlook 315
13.5	Conclusion and Outlook 919
15.5	References 315
13.5	References 315
14	References 315 Targeting CCR1 323 Pickard Haruk
13.3 14	References 315 Targeting CCR1 323 Richard Horuk Introduction 323
14 14.1	References 315 Targeting CCR1 323 <i>Richard Horuk</i> Introduction 323 <i>CCR1</i> as a Drug Target 324
14 14.1 14.2	References 315 Targeting CCR1 323 <i>Richard Horuk</i> Introduction 323 CCR1 as a Drug Target 324 CCR1 Antagonistr. 325
14 14.1 14.2 14.3 14.4	References 315 Targeting CCR1 323 <i>Richard Horuk</i> Introduction 323 CCR1 as a Drug Target 324 CCR1 Antagonists 325 Conclusions 323
14 .1 14.2 14.3 14.4	References 315 Targeting CCR1 323 <i>Richard Horuk</i> Introduction 323 CCR1 as a Drug Target 324 CCR1 Antagonists 325 Conclusions 333 Peferences 333
14 14.1 14.2 14.3 14.4	References 315 Targeting CCR1 323 <i>Richard Horuk</i> Introduction 323 CCR1 as a Drug Target 324 CCR1 Antagonists 325 Conclusions 333 References 333
14.1 14.2 14.3 14.4 15	References 315 Targeting CCR1 323 <i>Richard Horuk</i> Introduction 323 CCR1 as a Drug Target 324 CCR1 Antagonists 325 Conclusions 333 References 333 Targeting CCR3 339
14.1 14.2 14.3 14.4 15	References 315 Targeting CCR1 323 <i>Richard Horuk</i> Introduction 323 CCR1 as a Drug Target 324 CCR1 Antagonists 325 Conclusions 333 References 333 Targeting CCR3 339 <i>James Edward Pease</i>
14 14.1 14.2 14.3 14.4 15 15.1	References 315 Targeting CCR1 323 <i>Richard Horuk</i> Introduction 323 CCR1 as a Drug Target 324 CCR1 Antagonists 325 Conclusions 333 References 333 Targeting CCR3 339 <i>James Edward Pease</i> Introduction 339
14.1 14.2 14.3 14.4 15 15.1 15.2	References 315 Targeting CCR1 323 <i>Richard Horuk</i> Introduction 323 CCR1 as a Drug Target 324 CCR1 Antagonists 325 Conclusions 333 References 333 Targeting CCR3 339 <i>James Edward Pease</i> Introduction 339 CCR3 and the Eotaxin Family of Chemokines 339
14 14 .1 14 .2 14 .3 14 .4 15 15 .1 15 .2 15 .3	References 315 Targeting CCR1 323 <i>Richard Horuk</i> Introduction 323 CCR1 as a Drug Target 324 CCR1 Antagonists 325 Conclusions 333 References 333 Targeting CCR3 339 <i>James Edward Pease</i> Introduction 339 CCR3 and the Eotaxin Family of Chemokines 339 Structure–Function Studies of CCR3 and its Ligands 341
14.1 14.2 14.3 14.4 15 15.1 15.2 15.3 15.4	References 315 Targeting CCR1 323 <i>Richard Horuk</i> Introduction 323 CCR1 as a Drug Target 324 CCR1 Antagonists 325 Conclusions 333 References 333 Targeting CCR3 339 <i>James Edward Pease</i> Introduction 339 CCR3 and the Eotaxin Family of Chemokines 339 Structure–Function Studies of CCR3 and its Ligands 341 CCR3 and its Ligands in the Pathogenesis of Allergic Disease 341
14 14 .1 14 .2 14 .3 14 .4 15 15 .1 15 .2 15 .3 15 .4 15 .4 15 .4.1	References 315 Targeting CCR1 323 <i>Richard Horuk</i> Introduction 323 CCR1 as a Drug Target 324 CCR1 Antagonists 325 Conclusions 333 References 333 Targeting CCR3 339 <i>James Edward Pease</i> Introduction 339 CCR3 and the Eotaxin Family of Chemokines 339 Structure–Function Studies of CCR3 and its Ligands 341 CCR3 and its Ligands in the Pathogenesis of Allergic Disease 341 Supporting Evidence from Animal Models 342
14.1 14.2 14.3 14.4 15 15.1 15.2 15.3 15.4 15.4.1 15.4.2	References 315 Targeting CCR1 323 <i>Richard Horuk</i> Introduction 323 CCR1 as a Drug Target 324 CCR1 Antagonists 325 Conclusions 333 References 333 Targeting CCR3 339 <i>James Edward Pease</i> Introduction 339 CCR3 and the Eotaxin Family of Chemokines 339 Structure–Function Studies of CCR3 and its Ligands 341 CCR3 and its Ligands in the Pathogenesis of Allergic Disease 341 Supporting Evidence from Animal Models 342 Supporting Evidence from Clinical Studies 343
14 14 .1 14 .2 14 .3 14 .4 15 15 .1 15 .2 15 .3 15 .4 15 .4.1 15 .4.2 15 .5	References 315 Targeting CCR1 323 <i>Richard Horuk</i> Introduction 323 CCR1 as a Drug Target 324 CCR1 Antagonists 325 Conclusions 333 References 333 Targeting CCR3 339 <i>James Edward Pease</i> Introduction 339 CCR3 and the Eotaxin Family of Chemokines 339 Structure–Function Studies of CCR3 and its Ligands 341 CCR3 and its Ligands in the Pathogenesis of Allergic Disease 341 Supporting Evidence from Animal Models 342 Supporting Evidence from Clinical Studies 343 Targeting CCR3 Function 344
14.1 14.2 14.3 14.4 15 15.1 15.2 15.3 15.4 15.4.1 15.5 15.6	References 315 Targeting CCR1 323 <i>Richard Horuk</i> Introduction 323 CCR1 as a Drug Target 324 CCR1 Antagonists 325 Conclusions 333 References 333 Targeting CCR3 339 <i>James Edward Pease</i> Introduction 339 CCR3 and the Eotaxin Family of Chemokines 339 Structure–Function Studies of CCR3 and its Ligands 341 CCR3 and its Ligands in the Pathogenesis of Allergic Disease 341 Supporting Evidence from Animal Models 342 Supporting Evidence from Clinical Studies 343 Targeting CCR3 Function 344 Small-Molecule CCR3 Antagonists with <i>In Vivo</i> Activity 348
14.1 14.2 14.3 14.4 15 15.1 15.2 15.3 15.4 15.4.1 15.5 15.6 15.7	References 315 Targeting CCR1 323 <i>Richard Horuk</i> Introduction 323 CCR1 as a Drug Target 324 CCR1 Antagonists 325 Conclusions 333 References 333 Targeting CCR3 339 <i>James Edward Pease</i> Introduction 339 CCR3 and the Eotaxin Family of Chemokines 339 Structure–Function Studies of CCR3 and its Ligands 341 CCR3 and its Ligands in the Pathogenesis of Allergic Disease 341 Supporting Evidence from Animal Models 342 Supporting Evidence from Clinical Studies 343 Targeting CCR3 Function 344 Small-Molecule CCR3 Antagonists with <i>In Vivo</i> Activity 348 Summary 349
14.1 14.2 14.3 14.4 15 15.1 15.2 15.3 15.4 15.4.1 15.5 15.6 15.7	References 315 Targeting CCR1 323 <i>Richard Horuk</i> Introduction 323 CCR1 as a Drug Target 324 CCR1 Antagonists 325 Conclusions 333 References 333 Targeting CCR3 339 <i>James Edward Pease</i> Introduction 339 CCR3 and the Eotaxin Family of Chemokines 339 Structure–Function Studies of CCR3 and its Ligands 341 CCR3 and its Ligands in the Pathogenesis of Allergic Disease 341 Supporting Evidence from Animal Models 342 Supporting Evidence from Clinical Studies 343 Targeting CCR3 Function 344 Small-Molecule CCR3 Antagonists with <i>In Vivo</i> Activity 348 Summary 349 References 350

16 Chemokine Binding Proteins as Therapeutics 359

Ali Alejo and Antonio Alcami

- 16.1 Immune Modulation by Secreted Chemokine Binding Proteins (CKBPs) 359
- 16.2 Viral CKBPs (vCKBPs) 361
- 16.2.1 vCKBPs as Therapeutics 361
- 16.2.1.1 The Poxvirus 35-kDa Protein 361
- 16.2.1.2 The Gammaherpesvirus M3 Protein 362
- 16.2.1.3 The MYXV M-T7 Protein 363
- 16.2.2 Other vCKBPs 364
- 16.2.2.1 The Smallpox Virus-Encoded Chemokine Receptor (SECRET) Domain from Poxviruses 365
- 16.2.2.2 The Poxvirus A41 Protein 366
- 16.2.2.3 The Alphaherpesvirus Glycoprotein G (gG) 366
- 16.2.2.4 The Human Cytomegalovirus pUL21.5 Protein 366
- 16.3 The Schistosoma mansoni CKBP 366
- 16.4 Evasins, a Family of CKBPs from Ticks 367
- 16.5 Advantages and Limitations of the Use of CKBPs as Therapeutics 367 References 370

Index 375