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Edited by Martine J. Smit, Sergio A. Lira, and Rob Leurs

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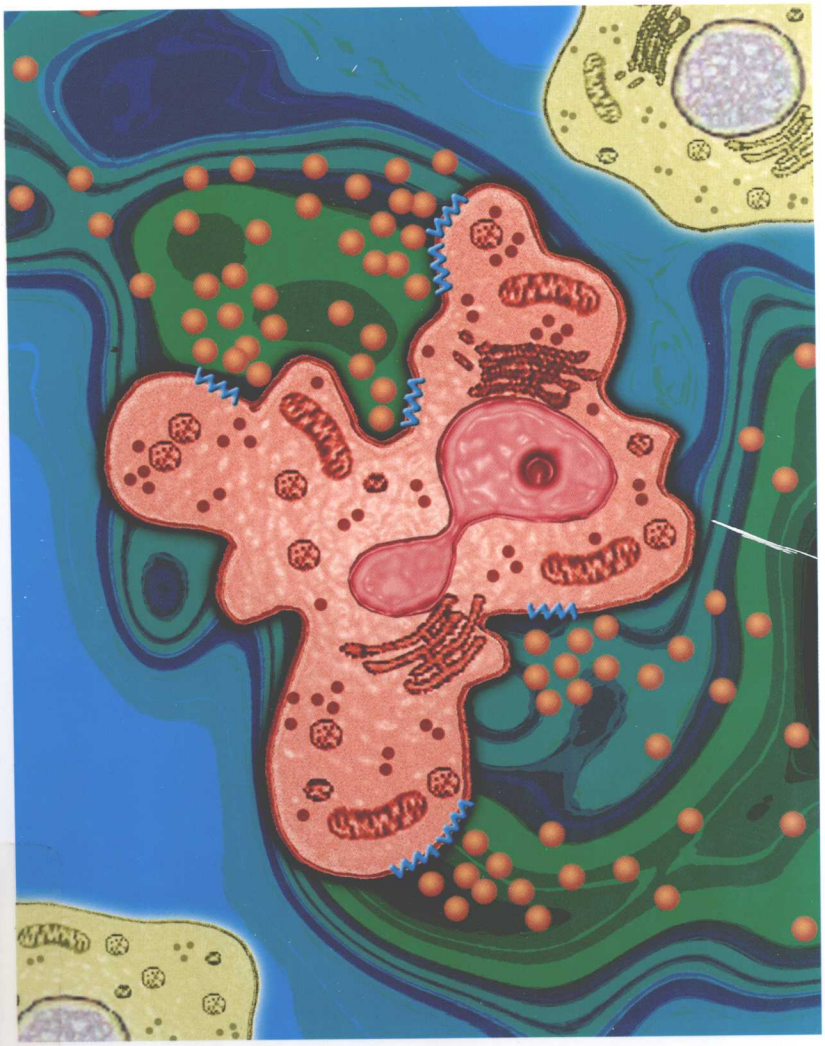
Chemokine Receptors as Drug Targets



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Chemokine Receptors as Drug Targets

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Preface

This volume is dedicated to the family of chemokine receptors, belonging to the class of G protein-coupled receptors (GPCRs). Chemokine receptors are primarily expressed on leukocytes, but are also present on cells of nonhematopoietic origin, such as endothelial cells and neurons. The chemokine receptor system is known to orchestrate various aspects of the immune system but also appears to control a variety of physiological processes. Excessive expression of chemokines and chemokine receptors and deregulated chemokine receptor function results in various disease states, including chronic inflammatory and vascular diseases and oncogenesis. Viruses have also taken advantage of the chemokine receptor system, indicating a role of this class of receptors in viral infection. The chemokine receptors CCR5 and CXCR4 are the two major co-receptors for HIV-1 entry into host cells. The pox- and herpesviruses express chemokines, chemokine-binding proteins and/or chemokine receptors, which may contribute to viral pathogenesis.

Since GPCRs are one of the most favored drug targets and the role of chemokine receptors in disease is becoming apparent, chemokine receptors are considered prime targets in drug research. The first successful small molecule targeting the chemokine receptor system was the CCR5 antagonist, for the prevention of HIV infection, approved by the FDA in 2007. The second small molecule (a CXCR4 antagonist) was approved by the FDA at the end of 2008 for hematopoietic stem cell mobilization. In the mean time the understanding of the chemokine receptor system is growing and several promising drugs are currently being tested in late-stage clinical trials.

The present volume by Martine Smit, Sergio Lira, and Rob Leurs is organized into three main sections, addressing fundamental, pathophysiological and drug discovery aspects of chemokine receptors. Following the philosophy of this series, authors from the different chapters come from academic institutions and pharmaceutical industry, fostering an active exchange between these two communities. The first section introduces the field of chemokines and their receptors, particularly referring to structural aspects. The second section focuses on the relevance of human and viral chemokine receptors in various diseases, such as inflammation, CNS diseases and cancer. The final section gives an overview of the currently available chemokine

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receptor ligands and their therapeutic impact. Six different chemokine receptor subtypes are particularly referred to. The last chapter comments on chemokine-binding proteins as therapeutics.

The series editors thank Martine Smit, Sergio Lira, and Rob Leurs for their enthusiasm to organize this volume and to work with such a fine selection of authors. We also express our thanks to Nicola Oberbeckmann-Winter, Waltraud Wüst, and Frank Weinreich from Wiley-VCH for their valuable contributions to this project and to the entire series.

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A Personal Foreword

The chemokine receptors, belonging to the family of G protein-coupled receptors are considered attractive targets for therapeutic intervention. Chemokines and their receptors play a prominent role in the development, homeostasis and activation of leukocytes in the innate and adapative immune system. Expression of chemokine receptors is not confined to leukocytes but is also apparent on cells of nonhematopoietic origin such as endothelial cells and neurons. Their excessive activity or dysfunction, however, is associated with the establishment of inflammation and diseases such as multiple sclerosis, inflammatory bowel disorder, arthritis and atherosclerosis. There is growing evidence that chemokine receptors play a role in cancer, including cancer metastasis and angiogenesis. Virus-encoded chemokines, chemokine receptors and chemokine scavengers have been identified, underscoring the importance of the chemokine system in viral pathogenesis. Besides chemokine receptors, CCR5 and CXCR4 have been shown to play profound roles in HIV pathogenesis through their ability to act as co-receptors for viral entry. This has led to the first approval by the FDA for a chemokine receptor antagonist for the prevention of HIV infection.

In the past decades much insight has been obtained on the structure of chemokines, the identification of their receptors and the mechanisms underlying the complex biologies in which they participate. This volume addresses the fundamental, pathophysiological and drug discovery aspects of chemokine receptors. The first part includes chapters that describe the fundamental aspects of chemokines and chemokine receptors. First, overviews are provided of the structure of chemokines and their receptors in relation to their biology and structural insights for homology modelling of chemokine receptors. The latest insights into the molecular mechanisms underlying chemokine-directed migration, a key event induced upon chemokine receptor activation, are presented. Besides the "classical" chemokine receptors, the biochemistry and biology of "atypical" chemokine receptors are explored and outlined. Last, the functional consequences and implications of homo/hetero dimerization of chemokine receptors are discussed.

The second part of this volume includes chapters that provide a comprehensive description of the role of the chemokine receptors in various diseases. The roles of

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various chemokines and chemokine receptors in chronic inflammatory diseases are outlined, including COPD, IBD, atherosclerosis and psoriasis. Thereafter, the role of the chemokine system in neurodegenerative diseases, including MS and EAE, brain ischemia and HIV-associated dementia, and in neuropathic pain is addressed. In addition, the latest insights into the role of chemokines and chemokine receptors in cancer metastasis are provided and potential roles of virus-encoded chemokine receptors are discussed. The final chapters discuss in detail different chemokine receptors, including CCR5, CXCR4, CXCR2, CXCR3, CCR1 and CCR3, as well as chemokine-binding proteins, with respect to therapeutical targeting and/or drug development.

Finally, we want to thank all authors of the different chapters from both academic institutions and the pharmaceutical industry for their valuable contributions. In addition, we want to acknowledge the pleasant collaboration with the series editor Dr. Raimund Mannhold as well as Dr. Frank Weinreich and Dr. Nicola Oberbeckmann-Winter from Wiley-VCH during the editing of this volume.

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