Preface

This is a remarkably timely volume for several distinct reasons. First, it captures an inflection point in the neurological consequences of the HIV pandemic. With the widespread use of highly active anti-retroviral therapy (HAART), devastating syndromes of HIV-associated dementia and vacuolar myelopathy have given way, respectively, to milder complications including cognitive impairment and painful peripheral neuropathy. The present book addresses mechanisms of these contemporary disorders. Second, there is an extensive discussion of pathways by which HIV infection, or its treatment, can lead to pain. Chemokines and their receptors constitute an integral part of this process, and this book contains the largest compilation to date, of concentrated information about the implication of chemokine biology in pain. Lastly, the book addresses chemokine receptor CXCR4 from multiple perspectives. This receptor and CXCL12, its ligand, participate in virtually every phase of biology from development, through organization and deployment of immune and nervous-system elements, infection, immunity, neurophysiology, adult neurogenesis, and functions of numerous tissue stem cells. The combination of these varied unique emphases renders this book highly topical.

Beginning Sect. I, *Kolson and colleagues* provide a measured consideration of a wide variety of research methods from magnetic resonance spectroscopy (MRS) to analysis of HIV proteins in in vitro systems. *Fischer-Smith and Rappaport* treat several overlapping topics, in effect yielding a "second opinion" about how to apply current research methods in the study of HIV-related neurological disease. *Tan*, *Hoke*, *and Nath* effectively and forcefully integrate clinical and pathogenetic data related to the crucial topic of HIV disease and peripheral neuropathy. *Wigdahl's* group contributes an authoritative and accessible treatment of HIV-viral latency embellished with well-designed graphics to illustrate complex concepts. *Klein and coworkers* combine a lucid review of chemokine receptors responsible for leukocyte trafficking with the presentation of a novel hypothesis, drawn from their research, about the role of CXCL12/CXCR4 as organizers of CNS perivascular infiltrates.

Section II opens with a fascinating discussion by *Vergote*, *Overall*, *and Power* on how proteolytic cleavage of CXCL12 by MMP2 mediates neurotoxicity via an aberrant ligand–receptor interaction with CXCR3. *Rostene et al*. provide a succinct summary of the role(s) of CXCR4 in activating nociceptors in the context of HIV

infection plus anti-retroviral agent treatment and also discuss the function(s) of CCL2/CCR2 in generating neuropathic pain. This latter topic is amplified in *Miller's* masterful discussion of CCR2 in neuropathic pain, in a chapter which also explains the roles of chemokine receptors in neural development and adult neurogenesis. *Khan* addresses the complex field of chemokine receptor interactions with cell-cycle regulatory components such as Rb and p53, as an entrée to comparing signaling to CXCR4 by HIV gp120 and the cardinal ligand CXCL12. *Rubin* contributes a subtle and comprehensive chapter on chemokine receptors in glioma, extending from cell biology to signaling to therapeutic application. *Bezzi et al.* discuss the critical issue of glutamate as a gliotransmitter, and places CXCR4 in the context of astrocyte regulation of synaptic activity. They incorporate unexpected roles of TNFα and prostaglandins as signaling intermediates, and also cover fully the topic of glutamate exocytosis by astrocytes, and its dysregulation during neuroinflammatory pathologies including HIV-associated cognitive impairment. *Limatola and colleagues* elegantly dissect how stimulation of CX3CR1 on microglia leads to adenosine production, which acts through A1R adenosine receptor on neurons, mediating neuroprotection.

Section III provides a very extensive and multifaceted treatment of the interactions between the chemokine and opioid system. These interactions affect the roles of chemokine receptors in pain, in HIV infections and immune-system functions, as well as in the emerging role of selected chemokines as neuromodulators/neurotransmitters – aspects that become particularly important when considering the prominent population of HIV-positive individuals who also abuse opiates. A contribution by *Roger's* group opens the section; these authors focus on their pioneering work regarding bidirectional communication between chemokine and opioid receptors in immune cells and address the relevance of these interactions to HIV infection. *Martin and Roy* discuss the major mechanisms of dysregulation of innate immunity by morphine and its implications for HIV progression, while providing interesting insights into the role of these mechanisms in wound healing. Next is a comprehensive review by *Hauser et al.* about the unique regulation of glial cells by opiates and a detailed dissection of the respective contribution of astroglia and microglia to HIV neuropathology in patients with history of drug abuse. This section is concluded by the work of *Sengupta and Meucci* introducing novel mechanisms implicated in negative modulation of neuronal CXCR4 by opiates, which significantly alter CXCR4-mediated signaling in the brain. This pathway may have significant consequences for the physiological actions of the CXCR4 receptor in the nervous system and may also promote disease progression.

These contributions represent major groups in this important field and fulfill a notable void in the current literature.

Ohio, USA Richard M. Ransohoff