

**Steven L. Kunkel, Nuria Godessart, Cory Hogaboam, Stephen W. Chensue and Nicholas Lukacs**

**Chemokines in animal models of inflammation**

**Summary**

The collective use of knockout, knock-in, and transgenic animals, along with viral delivered genes, neutralizing antibodies, antisense oligonucleotides, aptamers, and siRNA have all targeted various inflammatory mediators using a variety of murine models in an attempt to further our understanding of disease mechanisms. In the past decade there has been an explosion of data outlining the importance of individual chemokines to the initiation, maintenance, and resolution of inflammatory disease based on the use of well-developed animal models. These models have identified the importance of chemokine to both the innate immune response, as well as to the evolution of sophisticated acquired immunologic responses.

**Key words:** chemokines, cytokines, chemotaxis, arthritis, interstitial lung disease, granulomas, asthma, autoimmunity, inflammation, animal models

**Zamaneh Mikhak and Andrew D. Luster**

**Chemokines in allergic responses: eosinophils, basophils, mast cells**

**Summary**

Eosinophils, basophils and mast cells are cellular members of the innate immune system that play key roles in the generation of the allergic response in part through the function of their chemokines and chemokine receptors. They respond to the chemokines generated at sites of allergic inflammation and traffic to sites of allergen entry. Moreover, they augment allergic inflammation by releasing a variety of potent biological mediators, including many chemokines. Through their chemokines and chemokine receptors, eosinophils, basophils and mast cells contribute to the allergic response in three additional ways: they provide a link between innate and adaptive immune responses, skew T cell differentiation towards a Th2 phenotype and amplify the allergic response during viral infections.

**Key words:** eosinophils, basophils, mast cells, chemokines, chemokine receptors

**Zi-xuan Wang, Hirokazu Tamamura, Nicole Frilot, James Broach, Nobutaka Fujii and Stephen C. Peiper**

**Screening and characterization of cyclic pentapeptide CXCR4 antagonist/inverse agonist using a pheromone responsive reporter gene in *Saccharomyces cerevisiae*: Utility of G protein coupled receptor constitutively active mutants**

**Summary**

CXCR4, a G protein coupled receptor (GPCR) for stromal cell derived factor 1, also designated CXCL12, functions as a coreceptor for T-tropic (X4) strains of human immunodeficiency virus type 1 (HIV-1) infection and plays a critical role in programming the directed migration of tumor cells that results in metastatic spread. Thus it is a potential molecular target for these disorders. While candidate compounds that block CXCR4 have been tested in clinical trials, none is available with optimal pharmacologic properties. We have previously reported the expression of the human CXCR4 receptor in *Saccharomyces cerevisiae* and the derivation of signaling variants with constitutive activity. Here we

demonstrate the utility of applying this system to the screening and characterization of new generation CXCR4 antagonists derived from T140, a 14 residue polypeptide template. Screening an array of cyclic pentapeptides composed of 4 critical T140 residues and a glycine spacer yielded a lead compound that served as a foundation for enhancement of activity in three successive generations. While the third and fourth generation compounds had binding affinities similar to that of the T140 parental polypeptide, the potencies for inhibition of chemotaxis and cytosolic calcium mobilization induced by CXCL12 were less. The binding affinity of the cyclic pentapeptides for a specific constitutively active variant of CXCR4 showed excellent correlation with biologic potency. Screening compounds using GPCR variants that correspond to the active conformation may provide a better prediction of the biologic potency of lead compounds.

**Tassie L. Collins, Michael G. Johnson and Julio C. Medina**  
**Antagonists of CXCR3: a review of current progress**

**Summary**

The CXCR3 chemokine receptor is most prevalent on TH1 lymphocytes. CXCR3+ T lymphocytes are enriched at disease sites, most notably in the CSF and brain lesions of patients with multiple sclerosis, in rejecting transplant tissues, and in the synovium of rheumatoid arthritis patients. The three ligands for CXCR3 are CXCL9 (MIG), CXCL10 (IP-10) and CXCL11 (ITAC). These chemokines are upregulated by inflammatory cytokines such as IFN $\gamma$  and TNF $\alpha$  and their expression is elevated in a variety of inflammatory and autoimmune diseases. Thus, CXCR3 and its ligands represent attractive therapeutic targets for the treatment of human disease. In this article, we review the current progress that has been made toward developing antagonists of the CXCR3 pathway.

**Key words:** CXCR3, CXCL9, CXCL10, CXCL11, MIG, IP-10, ITAC, I-TAC  
CXCR3 antagonist

**Ronald P. Gladue and Matthew F. Brown**  
**Current status of CCR1 antagonists in clinical trials**

**Summary**

CCR1 and its ligands have been implicated in the pathogenesis of several disease processes by virtue of their ability to attract distinct subsets of leukocytes into sites of inflammation. This is supported by their increased expression at inflammatory sites and by numerous animal disease models where inhibition of CCR1 or its ligands have been shown to abrogate disease. These data prompted discovery efforts at several companies to identify small molecular weight CCR1 antagonists, two of which have now entered Phase II clinical trials: BX471 (Berlex / Schering AG) and CP-481,715 (Pfizer, Inc.). In this chapter we will review the evidence that supports a role for CCR1 in the pathogenesis of autoimmune diseases, the status of CCR1 antagonists in clinical trials, and the challenges involved in developing these agents.

**Key words:** CCR1, CCL3, CCL5, rheumatoid arthritis, multiple sclerosis, CP-481,715, BX471, ZK811792

**Paul J. Higgins, C. Eric Schwartz and Jean-Marie Nicolas**

**Small molecule CCR2 antagonists**

**Summary**

The status of the development of small molecule pharmacologic inhibitors of CCR2 is reviewed and the biologic characteristics of UCB's CCR2 antagonist, ucb-102405, described. A number of compound scaffolds have been patented, with Merck, AstraZeneca, Teijin, Telik, and Bristol-Meyers Squibb being major contributors. Some CCR2 antagonists were entered into clinical trials, though many of them have discontinued development. Validation of the therapeutic efficacy of this drug class is still needed, as no compounds have yet successfully completed phase II trials.

**Key words:** MCP-1, CCR2, chemokine, antagonist, inflammation, therapy, disease, drug development, clinical trials

**Louis M. Pelus and Hal E. Broxmeyer**

**Chemokine axes in hematopoietic stem cell mobilization**

**Summary**

Chemokines direct the movement of various leukocyte populations, including hematopoietic stem and progenitor cells. Chemokines and chemokine modulators can mobilize hematopoietic populations from marrow to peripheral blood where they can be used for transplantation to treat malignant and non-malignant disorders. This mobilization is rapid, occurring within minutes or hours after administration, rather than after days required for G-CSF or other cytokines. They also synergistically enhance mobilization responses when combined with the widely used clinical mobilizer, G-CSF. Mechanisms of mobilization may be associated with alterations in the CXCR4/SDF-1/CXCL12 axis. Their efficacy and rapid action make chemokines/chemokine modulators attractive agents to supplement mobilization by G-CSF, particularly in allogeneic transplants requiring high stem cell yields, or in patients and normal donors who mobilize poorly to G-CSF. In addition to combination mobilization, it is likely that in some cases, they may also have clinical mobilizing efficacy on their own, reducing the overall time and costs associated with peripheral blood stem cell transplantation.

**Key words:** chemokines, hematopoietic stem cell mobilization, peripheral blood stem cells, GRO $\beta$ /CXCL2, GRO $\beta$  $\Delta$ 4/CXCL2 $\Delta$ 4, IL-8, SDF-1/CXCL12, AMD3100

**Shon R. Pulley**

**CCR5 antagonists: from discovery to clinical efficacy**

**Summary**

It was 1996 when the chemokine receptor CCR5 was first cloned and identified as a member of the GPCR family. CCR5 is expressed in many tissues and is now implicated in a number of disease states. The role of CCR5 in HIV pathology triggered the push for discovering CCR5 antagonists with potential as therapeutic agents for the treatment of AIDS. Taking advantage of existing compound collections, a number of pharmaceutical companies took on the challenge of finding CCR5 antagonists. In the intervening decade, a number of antagonist efforts have faced the challenge of achieving in vivo potency while maintaining selectivity against off-target pharmacology. In addition to the potency and selectivity challenges,

considerable effort was expended around matching these features with the right pharmacokinetics. Pfizer's Maraviroc is currently in Phase III clinical trials with promising results achieved in earlier studies. The results of ongoing human efficacy trials are eagerly awaited not only by the AIDS patient population, but by all the researchers devoted to obtaining a safe and efficacious CCR5 antagonist.

**Key words:** CCR5, RANTES, MIP-1 $\alpha$ , antiviral, maraviroc, vicriviroc, aplaviroc, HIV, chemokine, chemokine receptor, antagonist, GPCR

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