Chemokines as Pharmacological Targets

Emanuela Galliera[a], Massimiliano M. Corsi[b,c,*], Raffaella Bonecchi[a,d], Massimo Locati[a,d] and Alberto Mantovani[a,d]

[a]*Laboratory of Leukocyte Biology and* [b]*Laboratory of Clinical Pathology, Institute of General Pathology, Medical Faculty, University of Milan, I-20133 Milan, Italy;* [c]*Laboratory of Biotechnological Applications, IRCCS Istituto Ortopedico Galeazzi, I-20161 Milan, Italy;* [d]*IRCCS Istituto Clinico Humanitas, I-20089 Rozzano, Italy*

Abstract: Chemokines play a key role in immune processes by controlling leukocyte recruitment in physiological and pathological condition. This review discusses the regulation of the chemokine system, its role in human diseases, and its potential relevance as a new pharmacological target.

Key Words: Chemokine, chemokine receptors, inflammation, GPCR inhibitors.

INTRODUCTION

Cytokines are important mediators in the pathogenesis of many human diseases, and have assumed growing relevance in clinical pathology as markers of disease onset, progression, and remission [1,2]. Among cytokines, chemokines, or "chemotactic cytokines", are particularly involved in the pathogenesis of several immuno-mediated human diseases [3] by virtue of their ability to coordinate leukocyte recruitment and activation. This review provides an overview of the chemokine system and its regulation, focusing on the clinical situations in which chemokines or their receptors might assume diagnostic value, and summarizes information on pharmacological tools recently developed to target this complex system.

1. The Chemokine System

Chemokines are a family of cytokines whose main biological function, as their name suggest, is to guide leukocyte migration to the site of inflammation [4]. They are a family of 42 small secreted proteins characterized by a conserved protein structure called "chemokines scaffold" strictly dependent on two conserved disulfide bonds connecting conserved cysteine residues, whose relative position determines the identification of four subfamilies [5-8]. In the CXC chemokine subfamily these cysteines are separated by a single intervening amino acid, while in the CC chemokine subfamily, the first two cysteine residues are in adjacent position. The C subfamily presents a single cysteine residue, and CX3C chemokines, with three residues separating the cysteine tandem. These subfamilies have also different location in the genome: most CC chemokines are coded by a large multigenic cluster on chromosome 17q11.2, while most of the CXC chemokines are coded by two large multigenic clusters on chromosome 4q21. C and CX3C chemokines are encoded by single genes located on chromosome 1q23, for the C chemokine and 16q13 for the CXC chemokine [9]. So far, 19 receptors have been defined, 10 for CC chemokines (CCR1 to 10), 7 for CXC chemokines (CXCR1 to 7), and 1 for C chemokines and CX3C chemokines (XCR1 and CX3CR1, respectively) [10,11].

Chemokines exert their biological function through their membrane receptors, which differently form other cytokine receptors are rhodopsin-like G protein-coupled receptors (GPCR). Different chemokine subfamilies act on their corresponding receptors expressed on different cell subtypes. The chemokine system is highly promiscuous, to provide flexibility and specificity in leukocyte trafficking, and pleiotropic, with a given chemokine acting on different leukocyte populations in order to coordinate the recruitment of different but functionally related leukocyte populations [12,13]. In general, neutrophils are attracted by CXC chemokines through CXCR1 and CXCR2; monocytes are mainly the major target of CC chemokines acting through CCR1, CCR2, and CCR5; Th1 and NK cells, mainly involved of type 1 inflammation, are attracted by to CXC chemokines through CXCR3 and to CX3CL1, acting through CX3CR1; Th2 and eosinophils, associated to type 2 inflammatory responses, are recreiuted by CCR3 and CCR4 agonists (Fig. **1**).

2. Regulation of the Chemokine system

Chemokines and their receptors form a complex system which undergoes different levels of regulation, ranging from chemokine production and processing, to receptor expression and coupling to G proteins (Fig. **2**). Depending on their regulation and production, chemokines can be distinguished in "homeostatic" chemokines, which control leukocyte homing and lymphocyte recirculation in normal conditions, and "inflammatory" chemokines, produced in response to inflammatory stimuli, like Tumour Necrosis Factor (TNF) α or Interferon (IFN) γ, in order to recruit leukocytes during inflammation (Fig. **2A**) [14]. Chemokines can also be considered molecular markers of different types of immune responses [15,16].

Extracellular processing of chemokines by proteases is an important way to regulate the activity and the function of the chemokine system in different physiological and pathological conditions [3,17-26]. For instance, CD26 cleaves the

*Address correspondence to this author at the Istituto di Patologia Generale, Università degli Studi di Milano, Via Luigi Mangiagalli 31, I-20133 Milano, Italy; Tel: +39-02.50315341; Fax: +39-02.50315338;
E-mail: mmcorsi@unimi.it

1389-5575/08 $55.00+.00 © 2008 Bentham Science Publishers Ltd.

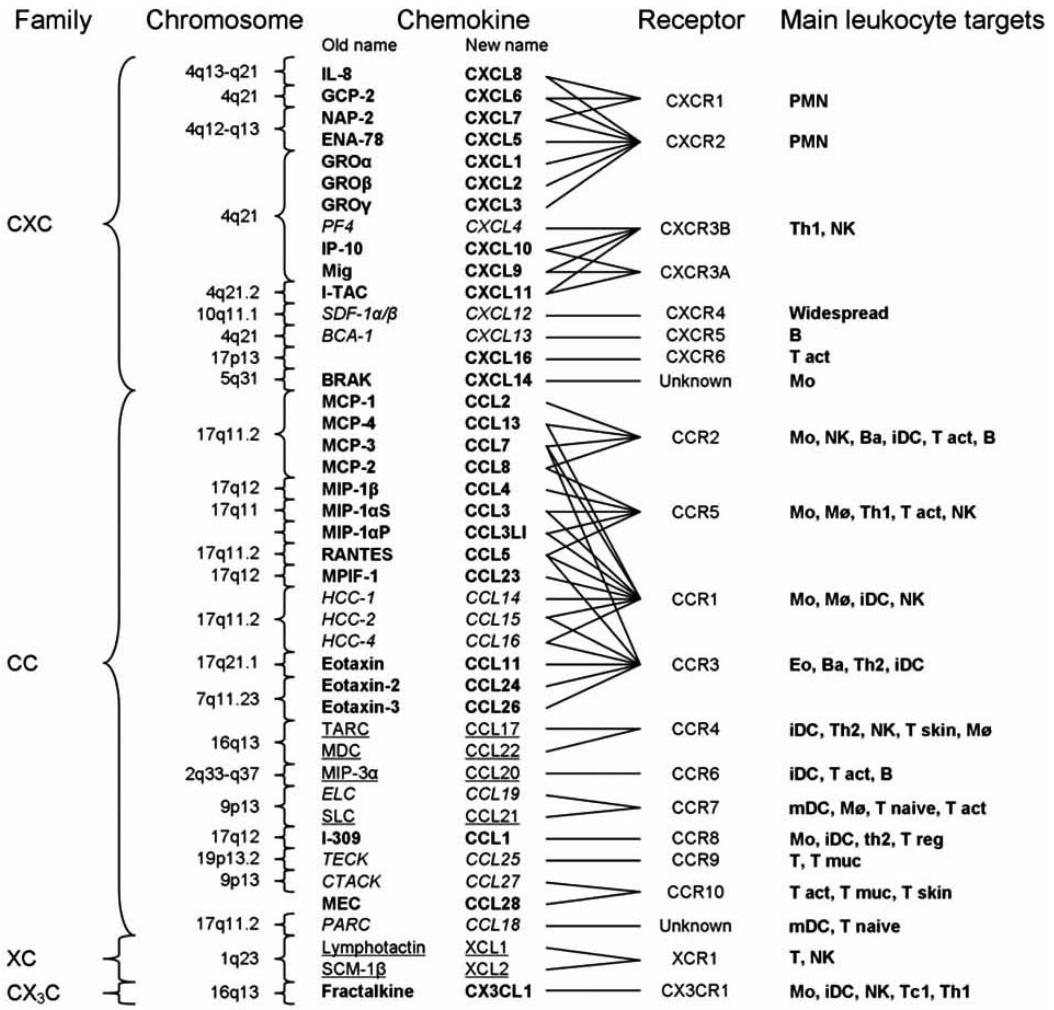

Fig. (1). The chemokine system: an overview.

Chemokines (family, chromosome location, and old and new nomenclature), their receptors, and predominant receptor repertoires in different leukocyte populations are listed. Names in bold identify inflammatory chemokines, names in italics homeostatic chemokines, underlined names refer to molecules belonging to both realms.

Chemokine acronyms are as follows: BCA, B cell activating chemokine; BRAK, breast and kidney chemokine; CTACK, cutaneous T-cell attracting chemokine; ELC, Epstein–Barr virus-induced receptor ligand chemokine; ENA-78, epithelial cell-derived neutrophils-activating factor (78 amino acids); GCP, granulocyte chemoattractant protein; GRO, growth-related oncogene; HCC, hemofiltrate CC chemokine; IP, IFN-inducible protein; I-TAC, IFN-inducible T-cell a chemoattractant; MCP, monocyte chemoattractant protein; MDC, macrophage derived chemokine; Mig, monokine induced by gamma interferon; MIP, macrophage inflammatory protein; MPIF, myeloid progenitor inhibitory factor; NAP, neutrophil-activating protein; PARC, pulmonary and activation-regulated chemokine; RANTES, regulated upon activation normal T cell-expressed and secreted; SCM, single C motif; SDF, stromal cell-derived factor; SLC, secondary lymphoid tissue chemokine; TARC, thymus and activation-related chemokine; TECK, thymus expressed chemokine.

Leukocyte acronyms are as follows: PMN, neutrophils; Eo, eosinophils; Ba, basophils; MC, mast cells; Mo, monocytes; Mø, macrophages; iDCs, immature dendritic cells; mDCs, mature DCs; T naive, naive T cells; T act, activated T cells; T skin, skin-homing T cells; T muc, mucosal-homing T cells; T reg, regulatory T cells.

CCR4-agonist CCL22 and generates two truncated forms of the chemokine, CCL22(3-69) and CCL22(5-69), with reduced capacity to interact with their cognate receptor CCR4, thus blocking Th2 recruitment (Fig. **2B**). The action of different chemokines is also controlled by the expression of chemokine receptors expression in that several receptors are detected exclusively in specific cell state [27,28]. Chemokine-receptors axis is can also be controlled al the level of receptor coupling to the G-protein. In certain conditions chemokine receptors are uncoupled by the signalling machinery, and are converted in functional decoys [29]. Moreover, beside 'canonical' chemokine receptors, which are usually coupled to intracellular signals leading to cell migration, a separated group of 'atypical' receptors, including the promiscuous receptor for CXC and CC chemokines DARC (Duffy Antigen Receptor for Chemokines), the decoy receptor selective for CC inflammatory chemokines D6, and the decoy receptor selective for CC homeostatic chemokines CCX CKR, have

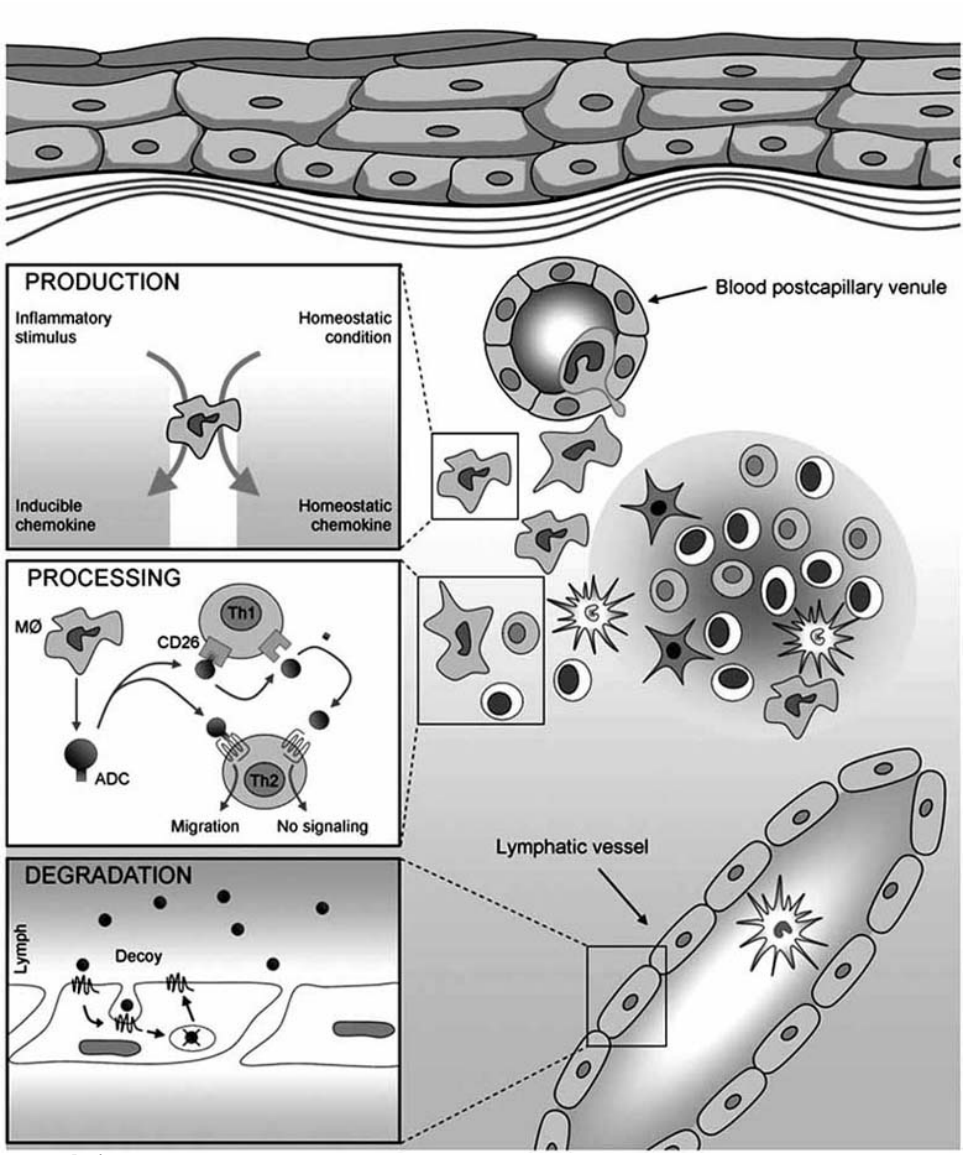

Fig. (2). Chemokine regulation.

Chemokine regulation occurs at various levels. In terms of production, homeostatic chemokines are constitutively expressed and control leukocyte homing in normal conditions, while inflammatory chemokines and their receptors undergo opposite regulation by pro- and anti-inflammatory mediators (A). In certain cases chemokines undergo post-translational processing by proteases, as exemplified by the Th1-mediated CD26-dependent processing of CCL22 that impairs receptor binding and strongly affects chemokine biological activity (B). Finally, chemokines can be internalized and degraded by chemokine decoy receptors, such as D6 receptor expressed on draining lymphatic vessels (C). During an inflammatory process these events act in a coordinated manner in order to finely tune the local inflammatory process and the lymph node reaction.

been described. These receptors bind their cognate ligand with high affinity and specificity but, differently from 'canonical' chemokine receptors, appear to be structurally uncoupled from G proteins, and do not induce any detectable intracellular signal after chemokine binding. Recent *in vivo* evidence clearly indicates that the biological function of this class of receptors is to compete with signalling receptors for the chemokine, sequester it, and target it to degradation, thus acting as negative regulators of inflammation. For this reason these previously referred to as "silent" receptors have been renamed chemokine *decoy* receptors (Fig. **2C**) [30].

3. The Role of Chemokines in Diseases

Chemokines and their receptors are major players in key events in immuno-mediated disorders, allowing leukocytes recruitment and sustaining acute and chronic inflammatory reactions. A number of animal models, genetic evidences, and clinical studies have now clearly shown the importance of chemokines and chemokine receptors in the pathogenesis of immune-mediated pathologies [31]. Studies in gene-targeted mice provided he formal demonstration of a non redundant role for inflammatory chemokines in leukocyte recruitment associated with acute and chronic inflammatory

responses first came from [32,33]. $CXCR2^{-/-}$ mice indicated a significant role of IL-8 in sustaining neutrophils-mediated inflammatory disease, showing that neutralization of the IL-8-CXCR1/2 axis resulted in almost complete protection from multiple inflammatory challenges. These results have been confirmed by pharmacologic inhibition of CXCR1 in humans [34-38]. Conversely, $CCR1^{-/-}$ and $CCR2^{-/-}$ mice present abnormal type I and type II responses, respectively, and altered granulomatous inflammation, and $CCR1^{-/-}$ mice also have reduced pancreatitis-associated pulmonary infiltration. $CCR5^{-/-}$ mice have enhanced delayed hypersensitivity reactions and increased humoral responses to T cell-dependent antigenic challenge. A considerable role for chemokines in host defence was suggested by gene-targeted animals have also demonstrated. For example, $CCR5^{-/-}$ mice and women with the inactivating CCR5 variant *Δ32-CCR5* display a host inflammatory response and develop complications after *Chlamydia trachomatis* infection of the genital tract [34,39], while $CXCR2^{-/-}$ and $CCR1^{-/-}$ mice display an increased susceptibility to *Aspergillus fumigatus*. In addition, $CCR5^{-/-}$ and $CCR2^{-/-}$ mice are more susceptible to infection with *Listeria monocytogenes*. Moreover, several evidence indicate a non redundant role of chemokine system in several autoimmune disorders, including rheumatoid arthritis (RA) [40], Sjogren syndrome [41], autoimmune thyroiditis [42], multiple sclerosis [43], psoriasis [44], and auto-immune uveoretinitis[45]. For example, patients with RA show a correlation between clinical disease activity and CCL2 and CCL5 levels, which have been proposed as markers of disease progression, and methotrexate treatment correlates with a reduction of CCL5 levels [46]. Similarly, elevated serum levels of CXCL10 have been associated with clinical disease activity in systemic lupus erythematosus [47], and CCR4 and its ligand CCL17 have been described to play a role in leukocytes recruitment in cutaneous lupus erythematosus [48].

Chemokines and chemokine receptors have been shown to affect several aspects of cancer development, including leukocyte infiltration, tumour growth, angiogenesis, and metastasis [49-52]. Different tumours present a different leukocyte infiltrate, recruited by the corresponding chemokines [53,54]. For example, a selective infiltration of $CCR5^{+}$ and $CXCR3^{+}$ T lymphocytes is present in human colorectal carcinoma [49], while $CXCR3^{+}$ B cells are found at elevated frequency in the peripheral blood of patients with MALT lymphoma [20]. Several clinical and epidemiological evidences suggest that chemokines can favour tumour development. As an example, in ovarian and breast cancers chemokine levels (CCL2 and CCL5) correlate with macrophage infiltration, lymph node metastasis and clinical aggressiveness [55,56]. Chemokine receptors also play a fundamental role in tumour progression and metastasis. Melanoma cells express high levels of CXCR2 and also constitutively produce its ligands CXCL1 and IL-8 that stimulates in an autocrine way proliferation and survival [57,58]. Similarly, prostate cancer cells and glioblastoma cells express both CXCR4 and CXCL12, thus stimulating their proliferation [59,60]. Tumor progression and metastasis involves CXCR4 in particular [61-64]. CXCR4 expression reflects tumor progression and regulates motility of bladder cancer cells [62], and it is also associated with lymph node metastasis in oral squamous cell carcinoma [63], human nasopharyngeal carcinoma [65], pancreatic cancer [66], non-small lung cancer [67], human colorectal cancer (in association with CCR7), and human breast cancer. Taken together, these data clearly demonstrates a relevant function of the chemokines system in several aspects of neoplastic diseases, with an emerging role of CXCL12/CXCR4 axis in the metastatic process.

Recent genetic evidences demonstrated that allelic variants of chemokines or chemokine receptors are associated to altered susceptibility and prognosis in human diseases. The first and most striking evidence came from the discovery that the *Δ32-CCR5* null allelic variant of the chemokine receptor and HIV-1 coreceptor CCR5 is associated with resistance to HIV-1 infection [68]. This allele has also effects kidney allograft survival [69,70], MS relapses [71], type I diabetes [72], and inflammatory bowel disease[73]. In addition to *Δ32-CCR5*, AIDS progressions is influenced by several other polymorphisms, including allelic variants in the CCL5 promoter and in the 3'-UTR region of CXCL12, both resulting in delayed disease progression and a prolonged survival in AIDS patients, and an allelic variant (V64I) of the minor HIV-1 coreceptor CCR2 [74]. This CCR2 allelic variant also influences the development of sarcoidosis and the progression of invasive cervical carcinoma. Other pathologies influenced in their development and outcome by chemokine polymorphisms include RA and polymorphism in CCR2 and CCR5, and the development of acute coronary syndrome and CX3CR1 polymorphic variants V249I and T280M [70,72, 75-78].

4. The Chemokine System as a Pharmacological Target

The prominent role of chemokines in immune-mediated diseases induced several pharmacological companies in the last decade to evaluate different strategies targeting the chemokine system, ranging from interference with chemokine production to receptor antagonism (Fig. **3**) [79,80].

The first pharmacological approach was based on the inhibition of chemokine production through classical anti-inflammatory drugs. For example, IL-8 and CCL2 production was found to be blocked by cyclosporine and FK506 [81,82], and molecules initially developed as cytokine inhibitors were also demonstrated to possess an inhibitory effect on chemokine production [83]. At present, chemokine production inhibition represents a promising but largely unexplored approach.

As for other cytokines, blocking antibodies interfering with the chemokine binding to their receptors have also been developed (Fig. **3**), and though the need for parenteral administration clearly represent a major limitation to the clinical use of these molecules [84,85], an anti-CCR2 blocking antibody is currently in phase I clinical trial [48].

The finding that chemokine receptors belong to the GPCR family, a class of receptors which represent the main target of the last 30 years of drug discovery, has focused the majority of efforts at the development of molecules interfering with receptor activation. This approach was initially strengthened by results obtained with chemokine variants. As mentioned, N-terminal CD26-mediated processing is one of the main chemokine inactivation mechanisms, and several

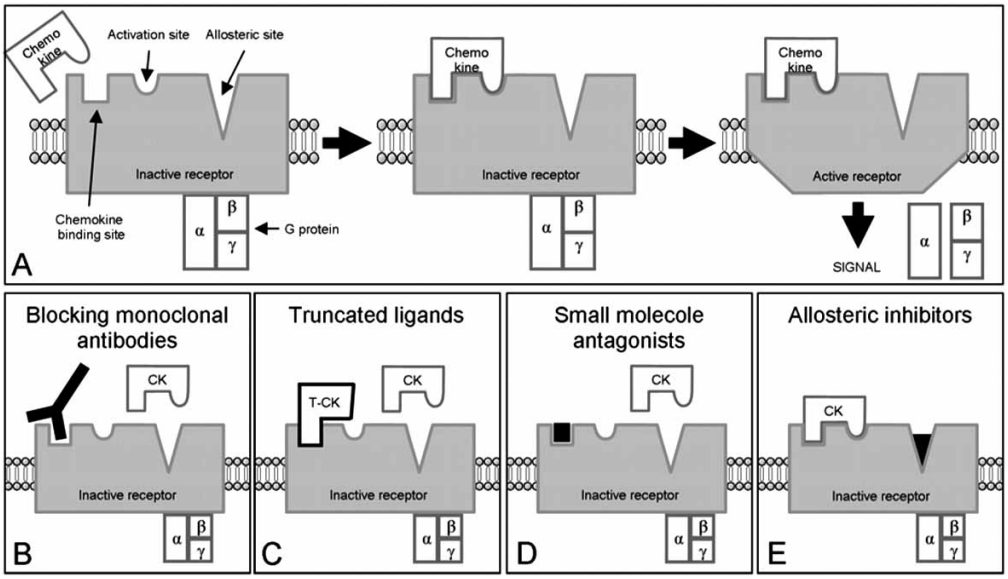

Fig. (3). Pharmacological inhibition of the chemokine system.

Chemokines exert their biological function through their G protein-coupled receptors. Chemokine receptor activation occurs in sequential steps. First, the chemokine core domain binds the N-terminal of the receptor, then the N-terminal of the chemokine interacts with a receptor activation site leading to receptor conformational changes and activation, and finally the activated receptor acts a GDP-GTP exchange factor for G proteins, which dissociate the alpha and beta-gamma subunits and activate intracellular signaling (A). Different pharmacological strategies can be used to interfere with this process. Blocking monoclonal antibodies sterically impair ligand binding (B), N-terminal truncated chemokines bind the receptor and compete with the biologically active full length ligand (C), and small molecule competitive antagonists compete with the chemokine for the binding site of the receptor (D). In all these cases, the ligand recognition is impaired. Receptor signaling can also be blocked by non-competitive inhibitors (E), which binds the receptor in an allosteric site preventing receptor conformational change and activation without interfering with chemokine binding.

N-truncated chemokines have been produced and proved to be able to interfere with receptor activation by full length agonists [3]. N-terminal modified chemokine variants have also been produced. The CCL5 variants Met-RANTES (presenting an additional methionine residue at the N-term) [86] and AOP-RANTES (with an amino-oxipenthane at the N-term) [87] have been shown to act as potent CCR3 antagonists (Fig. **3**).

These results paved the way to the search for small molecule receptor antagonists able to interfere with ligand recognition by the receptor (competitive inhibitors). Indeed, in the last ten years, chemokine receptor antagonists have been developed as new pharmacological tools for the therapy of different immune-mediates diseases, including asthma, atherosclerosis, and RA (Fig. **3** and Table **1**). As for several GPCRs, including receptors for somatostatin, tachykinin, neuropeptide Y, and cholecystokinin [88], a significant fraction of chemokine receptor inhibitors are represented by piperidine-containing compounds. This chemical group represents one of the most common templates identified for GPCRs, suggesting the existence of a conserved binding pocket within the transmembrane region of GPCRs, structurally related to the binding pocket occupied by retinal in the rhodopsin crystal structure [89]. Consistently with this, site-directed mutagenesis studies on several chemokine receptors have mapped the binding residues for chemokine receptor inhibitors in the immediate vicinity of the structurally conserved retinal-binding site of rhodopsin [90-95]. A second common feature of these compounds is the presence of a basic group, of different chemical nature in the different classes, suggesting an interaction with a negatively charged region of the receptor target. Consistently with this, most chemokine receptors contain an acidic residue in the upper third of the transmembrane helix (TM) 7, and at least for spiroperidine-based CCR2 antagonists a direct interaction with E291 has been demonstrated [96]. Small molecule antagonists targeting several chemokine receptors are under development by many companies (for a recent review see ref. [97,98] and the reference therein). For instance, a number of CCR1 antagonist have been developed, the most potent of which showed activity in murine models of multiple sclerosis, heart transplant rejection and renal fibrosis [99]. CCR2 is also a target for the development of small molecule antagonists, in particular for the treatment of chronic inflammatory diseases [65]. The most relevant target is represented by CCR5, for which several antagonists have been developed by a number of different companies as anti-HIV therapeutics, and are currently under phase II development [100] [98]. In the same field, a CXCR4 selective inhibitor which blocks replication of X4 strains of HIV-1 by binding to CXCR4 has been developed and subsequently substituted by a derivative for cardiotoxicity [101]. Interestingly, mutational analysis of CXCR4 identified a crucial role of three acidic residues in TM4 and TM6 and mapped the binding pocket of this inhibitor. This features could be recreated in the structurally distinct CXCR3, confirming the existence of a common binding site for these compound in chemokine receptors [102,103] (Table **1**).

Table 1. Chemokine Small Molecule Antagonists

COMPOUND	Mechanism	Receptor	Diseases	Phase	Ref.
UCB-35625 (Banyu)	Allosteric	CCR1/CCR3	Allergic diseases	I	113
BTX471 (Berlex)	Competitive	CCR1	MS, renal fibrosis	II	98
INCB-3284 (Incyte)	Competitive	CCR2	RA	I	65
766994 (Glaxo-Smith-Kline)	Competitive	CCR3	Asthma, allergic diseases	II	96, 97, 99
Sch-C (Schering-Pluogh)	Competitive	CCR5	AIDS, cancer	II	96, 97, 99
Sch-D (Schering Plough)	Competitive	CCR5	AIDS, cancer	I	96, 97, 99
TAK-799 (Takeda)	Competitive	CCR5	AIDS, cancer	II	96, 97, 99
873140 (Glaxo-Smith-Kline)	Competitive	CCR5	AIDS, cancer	II	96, 97, 99
UK-427857 (Pfizer)	Competitive	CCR5	AIDS, cancer	IV	96, 97, 99
Reparixin (Dompè)	Allosteric	CXCR1/CXCR2	RI injury	II	110
656933 (Glaxo-Smith-Kline)	Competitive	CXCR2	COPD	I	96, 97
T-487 (Amgen)	Competitive	CXCR3	MS,RA, psoriasis, organ transplant	II	96, 97
AMD3100 (Anormed)	Competitive	CXCR4	AIDS, cancer, bone marrow transplant	IV	100-102

A new emerging class of inhibitors is represented by allosteric non competitive receptor inhibitors. These molecules are able to bind the receptor in the allosteric site, distinct from the receptor binding site recognized by the ligand (orthosteric site) [104,105] thus locking the receptor in an inactive form without displacing the chemokine and prevents downstream signalling in terms of G protein activation, intracellular calcium mobilization, and chemotaxis. Allosteric inhibitors usually display high binding selectivity, avoiding the risk of cross-reactivity with others GPCRs [106-108], and a wider modulation of receptor activity, thus representing an interesting pharmacological tool to regulate receptor activities [109,110] (Fig. **3** and Table **1**). The first example of this type in the chemokine system is an inhibitor of the IL-8 receptors CXCR1 and CXCR2 which inhibits neutrophils recruitment in several *in vivo* animal models and is at present under phase II development for post-reperfusion damage prevention [111]. The identification of the interaction site of this molecule on CXCR1 represents a potential model for the development of other chemoattractant receptors allosteric antagonists, as a general strategy to modulate the activity of these receptors [112,113]. A second compound acting at least partially through an allosteric mechanism has reported to target CCR1 and CCR3, thus preventing eosinophil response to CCL3, CCL13, and CCL11, and it has been candidate for the treatment of allergic diseases [95,111,112,114].

CONCLUSION

The chemokine system plays a crucial role in innate immunity and in the inflammatory responses. This complex system is regulated at multiple levels, including chemokine production and processing, chemokine-receptor interaction, and receptor signalling. Data obtained with gene-targeted animals indicate that although *in vitro* this complex system is characterized by an important degree of redundancy, *in vivo* specificity for different pathologies do exists, and several evidences have now linked chemokines to most common

human diseases. These data have candidate the chemokine system as a new target for pharmacological therapy, making the development of small molecule chemokine receptor antagonists a main target of the pharmacological industry in the last years.

ABBREVIATIONS

TNF = Tumour Necrosis Factor

IFN = Interferon

DARC = Duffy Antigen Receptor for Chemokines

RA = rheumatoid arthritis

CCL = CC chemokine ligand

CXCL = CXC chemokine ligand

CX3CL = CX3C chemokine ligand

XCL = C chemokine ligand

CCR = CC chemokine receptor

CXCR = CXC chemokine receptor

CX3CR = CX3C chemokine receptor

XCR = C chemokine receptor

GPCR = G protein-coupled receptor

REFERENCES

[1] Bienvenu, J.; Monneret, G.; Fabien, N.; Revillard, J. P. *Clin. Chem. Lab. Med.*, **2000**, *38*, 267.

[2] Gerard, C.; Rollins, B. J. *Nat. Immunol.*, **2001**, *2*, 108.

[3] Baggiolini, M.; Dewald, B.; Moser, B. *Annu. Rev. Immunol*., **1997**, *15,* 675.

[4] Locati, M.; Murphy, P. M. *Annu. Rev. Med*., **1999**, *50*, 425.

[5] Rossi, D.; Zlotnik, A. *Annu. Rev. Immunol.*, **2000**, *18,* 217.

[6] Rollins, B. J. *Blood*, **1997**, *90*, 909.

[7] Allavena, P.; Sica, A.; Vecchi, A.; Locati, M.; Sozzani, S.; Mantovani, A. *Immunol. Rev.*, **2000**, *177,* 141.

[8] Sozzani, S.; Bonecchi, R.; D'Amico, G.; Frascaroli, G.; Vecchi, A.; Allavena, P.; Mantovani, A. *Eur. Cytokine Netw.*, **2000**, *11,* 502.

[9] Murphy, P. M.; Baggiolini, M.; Charo, I. F.; Hebert, C. A.; Horuk, R.; Matsushima, K.; Miller, L. H.; Oppenheim, J. J.; Power, C. A. *Pharmacol. Rev.*, **2000**, *52,* 145.

[10] Ahuja, S. K.; Gao, J. L.; Murphy, P. M. *Immunol. Today*, **1994**, *15,* 281.

[11] Horuk, R. *Cytokine Growth Factor Rev.*, **2001**, *12,* 313.

[12] Luster, A. D. *N. Engl. J. Med*., **1998**, *338,* 436.

[13] Mackay, C. R. *Nat. Immunol.*, **2001**, *2*, 95.

[14] Mantovani, A. *Immunol. Today*, **1999**, *20,* 254.

[15] Mantovani, A.; Allavena, P.; Sozzani, S.; Vecchi, A.; Locati, M.; Sica, A. *Semin. Cancer Biol.*, **2004**, *14*, 155.

[16] Mantovani, A.; Sica, A.; Sozzani, S.; Allavena, P.; Vecchi, A.; Locati, M. *Trends Immunol.*, **2004**, *25*, 677.

[17] Furie, M. B.; Randolph, G. J. *Am. J. Pathol*., **1995**, *146*, 1287.

[18] Struyf, S.; Proost, P.; Van Damme, J. *Adv. Immunol*., **2003**, *81*, 1.

[19] Loetscher, P.; Gong, J. H.; Dewald, B.; Baggiolini, M.; Clark-Lewis, I. *J. Biol. Chem.*, **1998**, *273*, 22279.

[20] Hensbergen, P. J.; van der Raaij-Helmer, E. M.; Dijkman, R.; van der Schors, R. C.; Werner-Felmayer, G.; Boorsma, D. M.; Scheper, R. J.; Willemze, R.; Tensen, C. P. *Eur. J. Biochem*., **2001**, *268*, 4992.

[21] Kraft, K.; Olbrich, H.; Majoul, I.; Mack, M.; Proudfoot, A.; Oppermann, M. *J. Biol. Chem*., **2001**, *276*, 34408.

[22] Proost, P.; De Meester, I.; Schols, D.; Struyf, S.; Lambeir, A. M.; Wuyts, A.; Opdenakker, G.; De Clercq, E.; Scharpe, S.; Van Damme, J. *J. Biol. Chem*., **1998**, *273*, 7222.

[23] Proost, P.; Struyf, S.; Couvreur, M.; Lenaerts, J. P.; Conings, R.; Menten, P.; Verhaert, P.; Wuyts, A.; Van Damme, J. *J. Immunol*., **1998**, *160*, 4034.

[24] Proost, P.; Struyf, S.; Schols, D.; Durinx, C.; Wuyts, A.; Lenaerts, J. P.; De Clercq, E.; De Meester, I.; Van Damme, J. *FEBS Lett*., **1998**, *432*, 73.

[25] Struyf, S.; De Meester, I.; Scharpe, S.; Lenaerts, J. P.; Menten, P.; Wang, J. M.; Proost, P.; Van Damme, J. *Eur. J. Immunol*., **1998**, *28*, 1262.

[26] Proost, P.; Struyf, S.; Van Damme, J. *Biochem. Soc. Trans*., **2006**, *34*, 997.

[27] Sallusto, F.; Lanzavecchia, A. *Immunol. Rev.*, **2000**, *177,* 134.

[28] Sallusto, F.; Mackay, C. R.; Lanzavecchia, A. *Annu. Rev. Immunol*., **2000**, *18*, 593.

[29] D'Amico, G.; Frascaroli, G.; Bianchi, G.; Transidico, P.; Doni, A.; Vecchi, A.; Sozzani, S.; Allavena, P.; Mantovani, A. *Nat. Immunol.*, **2000**, *1*,387.

[30] Mantovani, A.; Bonecchi, R.; Locati, M. *Nat. Rev. Immunol*., **2006**, *6*, 907.

[31] Locati, M.; Bonecchi, R.; Corsi, M. M. *Am. J. Clin. Pathol.*, **2005,** *123 Suppl, S82.*

[32] Brenier-Pinchart, M. P.; Pelloux, H.; Derouich-Guergour, D.; Ambroise-Thomas, P. *Trends Parasitol.*, **2001**, *17*, 292.

[33] Mahalingam, S.; Karupiah, G. *Immunol. Cell. Biol.*, **1997**, *77*, 469.

[34] Barr, E. L.; Ouburg, S.; Igietseme, J. U.; Morre, S. A.; Okwandu, E.; Eko, F. O.; Ifere, G.; Belay, T.; He, Q.; Lyn, D.; Nwankwo, G.; Lillard, J.; Black, C. M.; Ananaba, G. A. *J. Microbiol. Immunol. Infect.*, **2005**, *38*, 244.

[35] Casilli, F.; Bianchini, A.; Gloaguen, I.; Biordi, L.; Alesse, E.; Festuccia, C.; Cavalieri, B.; Strippoli, R.; Cervellera, M. N.; Di Bitondo, R.; Ferretti, E.; Mainiero, F.; Bizzarri, C.; Colotta, F.; Bertini, R. *Biochem Pharmacol*., **2005**, *69*, 385.

[36] Emadi, S.; Clay, D.; Desterke, C.; Guerton, B.; Maquarre, E.; Charpentier, A.; Jasmin, C.; Le Bousse-Kerdiles, M. C. *Blood*, **2005**, *105*, 464.

[37] Pignatti, P.; Moscato, G.; Casarini, S.; Delmastro, M.; Poppa, M.; Brunetti, G.; Pisati, P.; Balbi, B. *J. Allergy Clin. Immunol*., **2005**, *115*, 88.

[38] Van Damme, J.; Proost, P.; Lenaerts, J. P.; Opdenakker, G. *J. Exp. Med*., **1992**, *176*, 59.

[39] Hardison, J. L.; Wrightsman, R. A.; Carpenter, P. M.; Kuziel, W. A.; Lane, T. E.; Manning, J. E. *Infect. Immun*., **2006**, *74*, 135.

[40] Prahalad, S. *Genes Immun.* , **2006**, *7*, 264.

[41] Petrek, M.; Kolek, V.; Szotkowska, J.; du Bois, R. M. *Eur. Respir. J*., 2006, *20*, 1206.

[42] Chen, K.; Wei, Y.; Alter, A.; Sharp, G. C.; Braley-Mullen, H. *J. Leukoc. Biol*., **2005**, 78, 716.

[43] Tanuma, N.; Sakuma, H.; Sasaki, A.; Matsumoto, Y. *Acta Neuropathol. (Berl.)*, **2006**, *112*, 195.

[44] Szekanecz, Z.; Szucs, G.; Szanto, S.; Koch, A. E. *Curr. Drug Targets*, **2006**, *7*, 91.

[45] Takeuchi, A.; Usui, Y.; Takeuchi, M.; Hattori, T.; Kezuka, T.; Suzuki, J.; Okunuki, Y.; Iwasaki, T.; Haino, M.; Matsushima, K.; Usui, M. *Invest. Ophthalmol. Vis. Sci.*, **2005**, *46*, 3753.

[46] Ueno, A.; Yamamura, M.; Iwahashi, M.; Okamoto, A.; Aita, T.; Ogawa, N.; Makino, H. *Rheumatol. Int.*, **2005**, *25*, 361.

[47] Narumi, S.; Takeuchi, T.; Kobayashi, Y.; Konishi, K. *Cytokine*, **2000**, *12*, 1561.

[48] Bruhl, H.; Cihak, J.; Schneider, M. A.; Plachy, J.; Rupp, T.; Wenzel, I.; Shakarami, M.; Milz, S.; Ellwart, J. W.; Stangassinger, M.; Schlondorff, D.; Mack, M. *J. Immunol*., **2004**, *172*, 890.

[49] Musha, H.; Ohtani, H.; Mizoi, T.; Kinouchi, M.; Nakayama, T.; Shiiba, K.; Miyagawa, K.; Nagura, H.; Yoshie, O.; Sasaki, I. *Int. J. Cancer*, **2005**, *116*, 949.

[50] Johrer, K.; Zelle-Rieser, C.; Perathoner, A.; Moser, P.; Hager, M.; Ramoner, R.; Gander, H.; Holtl, L.; Bartsch, G.; Greil, R.; Thurnher, M. *Clin. Cancer Res.*, **2005**, *11,* 2459.

[51] Scala, S.; Ottaiano, A.; Ascierto, P. A.; Cavalli, M.; Simeone, E.; Giuliano, P.; Napolitano, M.; Franco, R.; Botti, G.; Castello, G. *Clin. Cancer Res.*, **2005**, *11*, 1835.

[52] Walser, T. C.; Fulton, A. M. *Breast Dis.*, **2004**, *20*, 137.

[53] Kulbe, H.; Levinson, N. R.; Balkwill, F.; Wilson, J. L. *Int. J. Dev. Biol*., **2004**, *48*, 489.

[54] Liu, A.; Nakatsuka, S.; Yang, W. I.; Kojya, S.; Aozasa, K. *Oncol. Rep.*, **2005**, *13*, 613.

[55] Monti, P.; Leone, B. E.; Marchesi, F.; Balzano, G.; Zerbi, A.; Scaltrini, F.; Pasquali, C.; Calori, G.; Pessi, F.; Sperti, C.; Di Carlo, V.; Allavena, P.; Piemonti, L. *Cancer Res.*, **2003**, *63*, 7451.

[56] Singh, K. K.; Hughes, M. D.; Chen, J.; Spector, S. A. *J. Infect. Dis*., **2005**, *191*, 1971.

[57] Lean, J. M.; Murphy, C.; Fuller, K.; Chambers, T. J. *J. Cell. Biochem*., **2002**, *87*, 386.

[58] Numasaki, M.; Watanabe, M.; Suzuki, T.; Takahashi, H.; Nakamura, A.; McAllister, F.; Hishinuma, T.; Goto, J.; Lotze, M. T.; Kolls, J. K.; Sasaki, H. *J. Immunol*., **2005**, *175*, 6177.

[59] Vaday, G. G.; Hua, S. B.; Peehl, D. M.; Pauling, M. H.; Lin, Y. H.; Zhu, L.; Lawrence, D. M.; Foda, H. D.; Zucker, S. *Clin. Cancer Res*., **2004**, *10*, 5630.

[60] Epstein, R. J. *Nat. Rev. Cancer*, **2004**, *4*, 901.

[61] Anders, H. J.; Vielhauer, V.; Frink, M.; Linde, Y.; Cohen, C. D.; Blattner, S. M.; Kretzler, M.; Strutz, F.; Mack, M.; Grone, H. J.; Onuffer, J.; Horuk, R.; Nelson, P. J.; Schlondorff, D. *J. Clin. Invest.*, **2002**, *109*, 251.

[62] Eisenhardt, A.; Frey, U.; Tack, M.; Rosskopf, D.; Lummen, G.; Rubben, H.; Siffert, W. *Eur. Urol.*, **2005**, *47*, 111.

[63] Ishikawa, T.; Nakashiro, K.; Hara, S.; Klosek, S. K.; Li, C.; Shintani, S.; Hamakawa, H. *Int. J. Oncol*., **2006**, *28*, 61.

[64] Schimanski, C. C.; Schwald, S.; Simiantonaki, N.; Jayasinghe, C.; Gonner, U.; Wilsberg, V.; Junginger, T.; Berger, M. R.; Galle, P. R.; Moehler, M. *Clin. Cancer Res.*, **2005**, *11,* 1743.

[65] Brodmerkel, C. M.; Huber, R.; Covington, M.; Diamond, S.; Hall, L.; Collins, R.; Leffet, L.; Gallagher, K.; Feldman, P.; Collier, P.; Stow, M.; Gu, X.; Baribaud, F.; Shin, N.; Thomas, B.; Burn, T.; Hollis, G.; Yeleswaram, S.; Solomon, K.; Friedman, S.; Wang, A.; Xue, C. B.; Newton, R. C.; Scherle, P.; Vaddi, K. *J. Immunol*., **2005**, *175*, 5370.

[66] Sato, N.; Matsubayashi, H.; Fukushima, N.; Goggins, M. *Cancer Biol. Ther*., **2005**, *4*, 70.

[67] Sun, Y. X.; Schneider, A.; Jung, Y.; Wang, J.; Dai, J.; Wang, J.; Cook, K.; Osman, N. I.; Koh-Paige, A. J.; Shim, H.; Pienta, K. J.; Keller, E. T.; McCauley, L. K.; Taichman, R. S. *J. Bone Miner. Res*., **2005**, *20*, 318.

[68] Lucotte, G. *Infect. Genet. Evol.*, **2002**, *1*, 201.

[69] Reiche, E. M.; Watanabe, M. A.; Bonametti, A. M.; Morimoto, H. K.; Morimoto, A. A.; Wiechmann, S. L.; Matsuo, T.; Miranda, H. C.; Reiche, F. V.; Oliveira, K. B. *Int. J. Immunogenet*., **2006**, *33*, 127.

[70] Yigit, B.; Bozkurt, N.; Berber, I.; Titiz, I.; Isbir, T. *Cell Biochem. Funct*., **2007** , *25* , 423.

[71] Favorova, O. O.; Andreewski, T. V.; Boiko, A. N.; Sudomoina, M. A.; Alekseenkov, A. D.; Kulakova, O. G.; Slanova, A. V.; Gusev, E. I. *Neurology* , **2002**, *59,* 1652.

[72] Mokubo, A.; Tanaka, Y.; Nakajima, K.; Watada, H.; Hirose, T.; Kawasumi, M.; Sakai, K.; Kanazawa, A.; Maeda, S.; Hosokawa, K.; Atsumi, Y.; Matsuoka, K.; Kawamori, R. *Diabetes Res. Clin. Pract*., **2006**, *73*, 89.

[73] Rector, A.; Vermeire, S.; Thoelen, I.; Keyaerts, E.; Struyf, F.; Vlietinck, R.; Rutgeerts, P.; Van Ranst, M. *Hum. Genet.*, **2001**, *108*, 190.

[74] Michael, N. L.; Louie, L. G.; Rohrbaugh, A. L.; Schultz, K. A.; Dayhoff, D. E.; Wang, C. E.; Sheppard, H. W. *Nat. Med.*, **1997**, *3*, 1160.

[75] Huerta, C.; Alvarez, V.; Mata, I. F.; Coto, E.; Ribacoba, R.; Martinez, C.; Blazquez, M.; Guisasola, L. M.; Salvador, C.; Lahoz, C. H.; Pena, J. *Neurosci. Lett*., **2004**, *370*, 151.

[76] Fenoglio, C.; Galimberti, D.; Lovati, C.; Guidi, I.; Gatti, A.; Fogliarino, S.; Tiriticco, M.; Mariani, C.; Forloni, G.; Pettenati, C.; Baron, P.; Conti, G.; Bresolin, N.; Scarpini, E. *Neurobiol. Aging*, **2004**, *25*, 1169.

[77] Niessner, A.; Marculescu, R.; Haschemi, A.; Endler, G.; Zorn, G.; Weyand, C. M.; Maurer, G.; Mannhalter, C.; Wojta, J.; Wagner, O.; Huber, K. *Thromb. Haemost*., **2005**, *93*, 949.

[78] Ohyauchi, M.; Imatani, A.; Yonechi, M.; Asano, N.; Miura, A.; Iijima, K.; Koike, T.; Sekine, H.; Ohara, S.; Shimosegawa, T. *Gut*, **2005**, *54*, 330.

[79] Sozzani, S.; Allavena, P.; Proost, P.; Van Damme, J.; Mantovani, A. *Prog. Drug Res.*, **1996**, *47*, 53.

[80] Zipfel, P. F.; Bialonski, A.; Skerka, C. *Biochem. Biophys. Res. Commun*., **1991**, *181,* 179.

[81] Meloni, F.; Cascina, A.; Paschetto, E.; Marone Bianco, A.; Morosini, M.; Pellegrini, C.; Fietta, A.; Vitulo, P.; Pozzi, E.; Vigano, M. *Transplant. Proc.*, **2003**, *35*, 1523.

[82] Wakabayashi, K.; Kambe, F.; Cao, X.; Murakami, R.; Mitsuyama, H.; Nagaya, T.; Saito, K.; Yoshida, J.; Seo, H. *Oncogene*, **2004**, *23*, 6924.

[83] Sironi, M.; Guglielmotti, A.; Polentarutti, N.; Fioretti, F.; Milanese, C.; Romano, M.; Vigini, C.; Coletta, I.; Sozzani, S.; Bernasconi, S.; Vecchi, A.; Pinza, M.; Mantovani, A. *Eur. Cytokine Netw.*, **1999**, *10*, 437.

[84] Arkin, M. R.; Randal, M.; DeLano, W. L.; Hyde, J.; Luong, T. N.; Oslob, J. D.; Raphael, D. R.; Taylor, L.; Wang, J.; McDowell, R. S.; Wells, J. A.; Braisted, A. C. *Proc. Natl. Acad. Sci. USA*, **2003**, *100*, 1603.

[85] Arkin, M. R.; Wells, J. A. *Nat. Rev. Drug. Discov*., **2004**, *3*, 301.

[86] Plater-Zyberk, C.; Hoogewerf, A. J.; Proudfoot, A. E.; Power, C. A.; Wells, T. N. *Immunol. Lett.* , **1997**, *57*, 117.

[87] Simmons, G.; Clapham, P. R.; Picard, L.; Offord, R. E.; Rosenkilde, M. M.; Schwartz, T. W.; Buser, R.; Wells, T. N.; Proudfoot, A. E. *Science*, **1997**, *276*, 5310.

[88] Flower, D. R. *Biochim. Biophys. Acta*, **1999**, *1422*, 207.

[89] Palczewski, K.; Kumasaka, T.; Hori, T.; Behnke, C. A.; Motoshima, H.; Fox, B. A.; Le Trong, I.; Teller, D. C.; Okada, T.; Stenkamp, R. E.; Yamamoto, M.; Miyano, M. *Science*, **2000**, *289*, 739.

[90] Dragic, T.; Trkola, A.; Thompson, D. A.; Cormier, E. G.; Kajumo, F. A.; Maxwell, E.; Lin, S. W.; Ying, W.; Smith, S. O.; Sakmar, T. P.; Moore, J. P. *Proc. Natl. Acad. Sci. USA*, **2000**, *97*, 5639.

[91] Gerlach, L. O.; Skerlj, R. T.; Bridger, G. J.; Schwartz, T. W. *J. Biol. Chem*., **2001**, *276*, 14153.

[92] Hatse, S.; Princen, K.; Gerlach, L. O.; Bridger, G.; Henson, G.; De Clercq, E.; Schwartz, T. W.; Schols, D. *Mol. Pharmacol*., **2001**, *60*, 164.

[93] Matthys, P.; Hatse, S.; Vermeire, K.; Wuyts, A.; Bridger, G.; Henson, G. W.; De Clercq, E.; Billiau, A.; Schols, D. *J. Immunol*., **2001**, *167*, 4686.

[94] Labrosse, B.; Brelot, A.; Heveker, N.; Sol, N.; Schols, D.; De Clercq, E.; Alizon, M. *J. Virol*.,**1998**, *72*, 6381.

[95] Sabroe, I.; Peck, M. J.; Van Keulen, B. J.; Jorritsma, A.; Simmons, G.; Clapham, P. R.; Williams, T. J.; Pease, J. E. *J. Biol. Chem.*, **2000**, *275*, 25985.

[96] Mirzadegan, T.; Diehl, F.; Ebi, B.; Bhakta, S.; Polsky, I.; McCarley, D.; Mulkins, M.; Weatherhead, G. S.; Lapierre, J. M.; Dankwardt, J.; Morgans, D.; Jr.; Wilhelm, R.; Jarnagin, K. *J. Biol. Chem*., **2000**, *275*, 25562.

[97] Allen, S. J.; Crown, S. E.; Handel, T. M. *Annu. Rev. Immunol*., **2007**, *25*, 787.

[98] Wells, T. N.; Power, C. A.; Shaw, J. P.; Proudfoot, A. E. *Trends Pharmacol. Sci.*, **2006**, *27*, 41.

[99] Vaidehi, N.; Schlyer, S.; Trabanino, R. J.; Floriano, W. B.; Abrol, R.; Sharma, S.; Kochanny, M.; Koovakat, S.; Dunning, L.; Liang, M.; Fox, J. M.; de Mendonca, F. L.; Pease, J. E.; Goddard, W. A.; 3rd, Horuk, R. *J. Biol. Chem*., **2006**, *281*, 27613.

[100] Ribeiro, S.; Horuk, R. *Pharmacol. Ther.*, **2005**, *107*, 44.

[101] Princen, K.; Schols, D. *Cytokine Growth Factor Rev.*, **2005**, *16*, 659.

[102] Hatse, S.; Princen, K.; Vermeire, K.; Gerlach, L. O.; Rosenkilde, M. M.; Schwartz, T. W.; Bridger, G.; De Clercq, E.; Schols, D. *FEBS Lett.*, **2003**, *546*, 300.

[103] Rosenkilde, M. M.; Gerlach, L. O.; Jakobsen, J. S.; Skerlj, R. T.; Bridger, G. J.; Schwartz, T. W. *J. Biol.Chem*., **2004**, *279*, 3033.

[104] Christopoulos, A.; Kenakin, T. *Pharmacol. Rev.*, **2002**, *54*, 323.

[105] Vauquelin, G.; Van Liefde, I. *Fundam. Clin. Pharmacol.*, **2005**, *19*, 45.

[106] Onuffer, J.; McCarrick, M. A.; Dunning, L.; Liang, M.; Rosser, M.; Wei, G. P.; Ng, H.; Horuk, R. *J. Immunol.*, **2003**, *170*, 1910.

[107] Onuffer, J. J.; Horuk, R. *Trends Pharmacol. Sci*., **2002**, *23*, 459.

[108] Pagliaro, L.; Felding, J.; Audouze, K.; Nielsen, S. J.; Terry, R. B.; Krog-Jensen, C.; Butcher, S. *Curr. Opin. Chem. Biol*., **2004**, *8*, 442.

[109] Lazareno, S.; Popham, A.; Birdsall, N. J. *J. Mol. Neurosci*., **2002**, *19*, 123.

[110] Proudfoot, A. E.; Power, C. A.; Wells, T. N. *Immunol.Rev*., **2000**, *177,* 246.

[111] Bertini, R.; Allegretti, M.; Bizzarri, C.; Moriconi, A.; Locati, M.; Zampella, G.; Cervellera, M. N.; Di Cioccio, V.; Cesta, M. C.; Gal-

liera, E.; Martinez, F. O.; Di Bitondo, R.; Troiani, G.; Sabbatini, V.; D'Anniballe, G.; Anacardio, R.; Cutrin, J. C.; Cavalieri, B.; Mainiero, F.; Strippoli, R.; Villa, P.; Di Girolamo, M.; Martin, F.; Gentile, M.; Santoni, A.; Corda, D.; Poli, G.; Mantovani, A.; Ghezzi, P.; Colotta, F. *Proc. Natl. Acad. Sci.USA*, **2004**, *101*, 11791.

[112] Moriconi, A.; Cesta, M. C.; Cervellera, M. N.; Aramini, A.; Coniglio, S.; Colagioia, S.; Beccari, A. R.; Bizzarri, C.; Cavicchia, M. R.; Locati, M.; Galliera, E.; Benedetto, P. D.; Vigilante, P.; Bertini, R.; Allegretti, M. *J. Med. Chem.*, **2007**, *50*,3984.

[113] Garau, A.; Bertini, R.; Mosca, M.; Bizzarri, C.; Anacardio, R.; Triulzi, S.; Allegretti, M.; Ghezzi, P.; Villa, P. *Eur. Cytokine Netw.*, **2006**, *17*, 35.

[114] Wise, E. L.; Duchesnes, C.; da Fonseca, P. C.; Allen, R. A.; Williams, T. J.; Pease, J. E. *J. Biol. Chem.*, **2007**, *282*, 27935.

Received: 24 August, 2007 **Revised: 15 January, 2008** **Accepted: 23 January, 2008**

Copyright of Mini Reviews in Medicinal Chemistry is the property of Bentham Science Publishers Ltd. and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.