

# Targeting chemokines: new drugs for old diseases

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*Chemokine receptor antagonists are set to become novel important pharmacological tools within the current therapeutic repertoire available for the management of various inflammatory conditions.*

Currently in various phases of drug development, these molecules act by inhibiting specific inflammatory pathways, and current research suggests a safer adverse effect profile for these drugs than today's therapy.<sup>1</sup>

## Introduction

Chemokines represent a large family of proteins that are produced by a variety of cells, including stromal cells, epithelial cells and immune cells. They are cell activators and chemoattractants, regulating the traffic of cells through a chemotactic gradient. They have a pivotal role in the trafficking of a variety of leukocytes such as T-lymphocytes and neutrophils and endothelial cells: (a) within primary lymphoid organs, (b) from primary to secondary lymphoid organs, (c) between secondary lymphoid organs, and (d) during a humoral immune response.<sup>2</sup> They therefore possess an essential role in both the inflammatory and immunological processes.

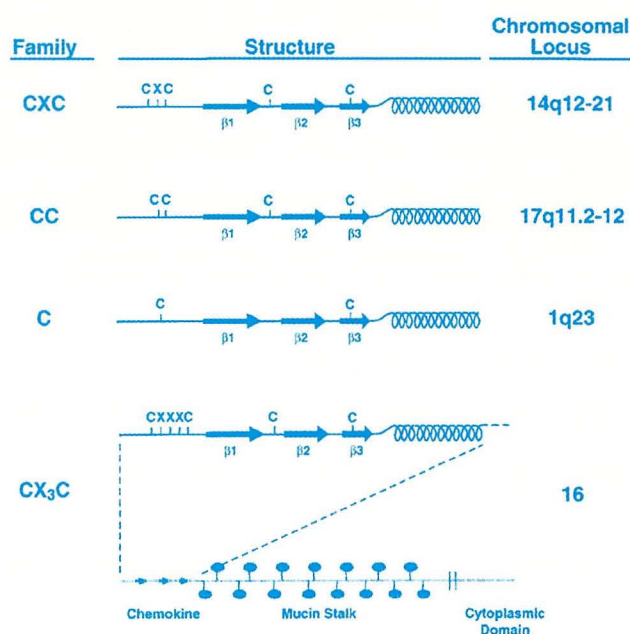
## Classification

Over forty human chemokines have been currently identified (Table 1), and these have been classified by structure into four sub-classes, according to the number and spacing of conserved cysteine residues in the chemotactic domain. These four sub-classes are given the preferred names C, CC, CXC and CXXXC, with CC possessing two cysteine residues adjacent to each other, CXC and CXXXC possessing one and three amino acids respectively between the cysteine residues and the C having one of the two cysteine residues missing (Figure 1)

Chemokine	Former designation	Receptor(s)
CCL3	MIP-1 $\alpha$	CCR1, CCR5
CCL5	RANTES	CCR1, CCR3, CCR5
CCL8	MCP-2	CCR1, CCR2, CCR3
CCL17	TARC	CCR4
CXCL12	SDF-1, PBSF	CXCR4

**Table 1:** Some chemokine ligands and their specific receptors

MIP-1 $\alpha$ : Macrophage inflammatory protein 1 alpha, RANTES: Regulated upon Activation, Normal T-cell Expressed, and Secreted, MCP-2: Macrophage chemoattractant protein 2, TARC: Thymus and activation-regulated chemokine, SDF-1: stromal cell-derived factor-1, PBSF: pre-B cell growth-stimulating factor.



**Figure 1:** The common structure and chromosomal location of the four chemokine sub-classes, showing the location of cysteine residues, after which they are named. All chemokines have at least three  $\beta$ -pleated sheets (indicated as  $\beta$ 1-3) and a C-terminal  $\alpha$ -helix. The CX3C chemokine domain occurs at the end of a long stalk which is heavily substituted with mucin-like carbohydrates. The protein is embedded in the membrane and has a short cytoplasmic domain. (Reproduced from Rollins, 1997.<sup>22</sup>)

## Chemokine receptors

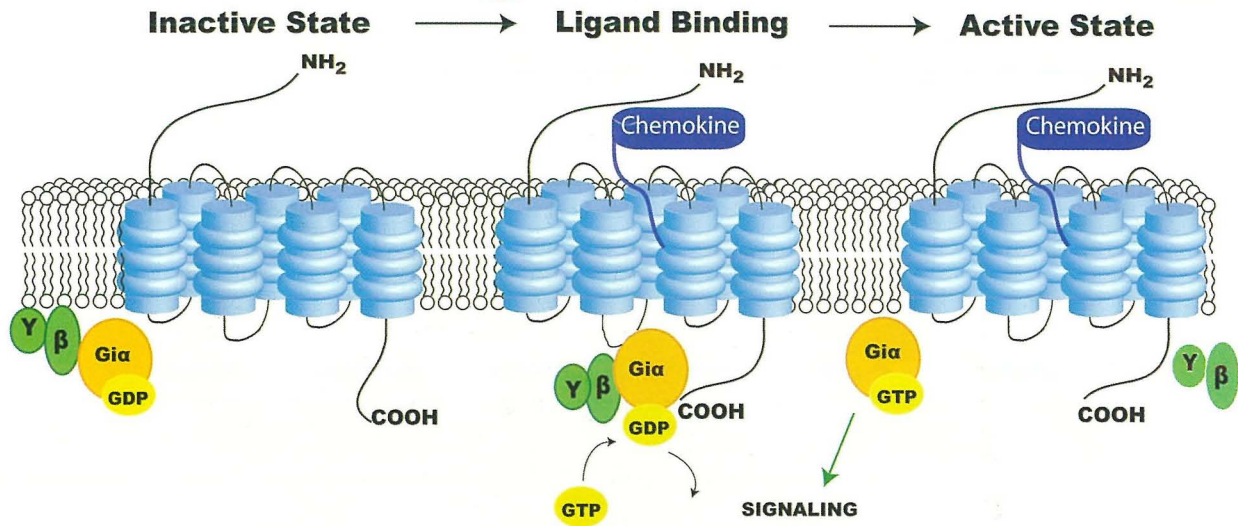
Chemokine receptors are structurally and functionally related proteins, that are members of the class A G-protein coupled receptors (GPCRs); they are all coupled to  $G_{\text{inhibitory}}$  proteins.<sup>3</sup>

Currently 18 proteins that meet the definition for a chemokine receptor exist, with each sub-family of the chemokine class of inflammatory mediators having its own sub-class of receptors. Of these 18 known proteins, 10 are known to be CCRs, 6 are CXCRs, and only one receptor is known for each of the CXXXC and C sub-classes (CXXXCR1 and XCR1 respectively).

Of all of these receptors, it is of interest to note that only the CXCR4 has been found to be essential for life.<sup>4</sup>

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**Figure 2: Chemokine receptor activation.** ( $G_{i\alpha}$ - $\beta\gamma$ : G-protein, GDP: Guanosine diphosphate, GTP: Guanosine- triphosphate. Adapted from O'Hayre *et al*, 2008.<sup>23</sup>)

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Chemokine receptors are commonly known to exhibit promiscuity,<sup>5</sup> that is, while certain chemokines show a preference for their own specific receptor; they may also interact with other receptors, causing activation. With the same idea, receptors themselves may also be activated by other, non-specific chemokines. This is known as the *shared receptor concept*, which occurs within, but not between the CC or CXC branches, except for the Duffy antigen/receptor for chemokine (DARC) which binds to the CC and CXC classes with equal affinity.<sup>6</sup> An example of this concept is the chemokine ligand MIP-1 $\alpha$  which binds with high affinity to CCR1, CCR3 and CCR5.

## Mode of action

Chemokines act by regulating leukocyte recruitment; causing cellular activation and inflammatory mediator release by promoting the Th<sub>2</sub> inflammatory response and by regulating the release of IgE. Their immunomodulatory and chemoattractant action occurs via the infiltration of inflammatory cells and by the inflammatory burst caused from eosinophils and basophils. This causes the migration of leukocytes, a critical component of systemic immunity, from the vascular compartment into the tissues through a process of chemotaxis. This highlights the importance of chemokines as inflammatory mediators as well as the significance of their receptors, the regulation of expression of which is

recognised as one of the key events in leukocyte localisation and trafficking during inflammation. Indeed, chemokine expression has been reported to play a major role in (a) glomerulonephritis, (b) inflammatory bowel disease, (c) allergenic transplant rejection, (d) atopic dermatitis, (e) allergic rhinitis, (f) asthma, and (g) chronic obstructive pulmonary disease.<sup>7</sup> This list further includes auto-immune disease such as diabetes and multiple sclerosis, stemming from the fact that chemokines are also able to direct immune cells to target and destroy perfectly healthy cells.

Therefore antagonism of various chemokine receptors has been proposed as a useful therapeutic approach in the management of inflammatory conditions, and indeed several such molecules are currently under development as novel therapeutic agents.<sup>8</sup>

## Chemokine receptor antagonists

The shared receptor concept may make it more beneficial for the pharmaceutical industry to design and produce receptor antagonists, rather than drugs that antagonise the chemokine ligands directly. Indeed various chemokine receptor antagonists are currently being developed as novel therapeutic tools for a variety of diseases. For example, CCR4 antagonists are currently under development for asthma therapeutics. High levels of the CCR4 ligands RANTES, MCP-1, TARC and MDC have been detected in both the

sputum and serum of asthmatics.<sup>9</sup> Antagonism of the CCR4, a receptor that has been determined to be a selective marker for Th<sub>2</sub> type lymphocytes,<sup>5,10</sup> has been shown to result in decreased eosinophilia and diminished airway hyperresponsiveness.<sup>11,12</sup>

It has been recently demonstrated that CCR4 antagonism may be used as a mechanism to inhibit the recruitment of activated leukocytes.<sup>13</sup> These CCR4 antagonists include the neutralising antibody 1G1, which has been shown to potentially block TARC binding to CCR4 transfectants and to prevent chemotaxis of these cells in response to MDC and TARC.<sup>7</sup> Also under development are spironolactams and spiroperidines,<sup>3</sup> a series of 2-aminothiazole derivatives aimed at inhibiting TARC and MDC binding to the CCR4,<sup>14</sup> as well as 2,4-diaminoquinazolines, whose administration in a murine model of acute dermatitis showed significant anti-inflammatory activity.<sup>15</sup>

Other antagonists include the pyrazolone methylamino piperidine derivatives and the patented product GW-766994, both CCR3 antagonists, the latter of which is currently undergoing Phase II clinical trials for the treatment of asthma and allergic rhinitis. Besides having CCR4 antagonistic activity, the spiroperidines also exert a very potent CCR2 blocking action,<sup>16</sup> while the CCR1 antagonist BX471 has been reported to be efficient in a rat heterotrophic heart transplant rejection model.<sup>17</sup>

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## Conclusion

Chemokine receptor antagonists therefore have a future in the treatment of inflammatory disease, not only since they seem to modify disease with minimal impact on normal host defence, but also since their action seems to be highly specific with few adverse effects.<sup>18</sup>

The shared receptor concept approach requires the development of antagonists that target a wide variety of receptors at the same time, whose potency would be dependent on the affinity to the receptor and its degree of antagonistic effect. This would avoid the use of complex antagonist mixtures.

Besides the future of chemokine receptor antagonists as anti-inflammatory agents and immunosuppressants, one must not fail to mention the advances other types of chemokine antagonists have had in other therapeutic fields. Chemokines have been found to be used by various intracellular pathogens, most notably HIV and *Plasmodium vivax* to facilitate their entry and transmission, and therefore they may represent novel antiviral and antiparasitic treatment. Indeed, TAK-779, the first reported non-peptide antagonist<sup>19</sup> is a CCR5 antagonist that has recently been in Phase I clinical trials as an anti-HIV treatment.<sup>20</sup> More recently reported CCR5 antagonists include UK 427857 (maraviroc),<sup>21</sup> approved by the European Medicines Agency in September 2007,

and SCH 351125 (vicriviroc), currently undergoing Phase II clinical trials,<sup>22</sup> all of which contribute to the antiviral therapeutic repertoire. 

## References

1. Chemokine Therapeutics Fact Sheet. Available at [http://www.chemokine.net/fact\\_sheet.htm](http://www.chemokine.net/fact_sheet.htm).
2. Melchers F, Rolink AG, Schaniel C. The Role of Chemokines in Regulating Cell Migration during Humoral Immune Responses. *Cell* 1999; 99:351-4.
3. Pease JE, Williams TJ. Chemokines and their receptors in allergic disease. *J Allergy Clin Immunol* 2006; 118:305-18.
4. Murphy PM, Baggiolini M, Charo IF *et al*. International Union of Pharmacology. XXII. Nomenclature for Chemokine Receptors. *Pharmacol Rev* 2000; 52:145-76.
5. Smit JJ, Lukacs NW. A closer look at chemokines and their role in asthmatic responses. *Eur J Pharmacol* 2006; 533:277-88.
6. Horuk R. Chemokine receptors. *Cytokine Growth Factor Rev* 2001; 12:313-35.
7. Chantry D, Burgess LE. Chemokines in Allergy. *Curr Drug Targets Inflamm Allergy* 2002; 1:109-16.
8. United States Trademark and Patent Office. Available at: <http://www.uspto.gov/>
9. Sekiya T, Yamada H, Yamaguchi M *et al*. Increased Levels of a TH2-type CC Chemokine Thymus and activation regulated chemokine (TARC) in serum and induced sputum of asthmatics. *Allergy* 2002; 57:173-7.
10. Peroni GD, Bordignon PP, Piacenti L.G *et al*. CC chemokine receptor expression in childhood asthma is influenced by natural allergen exposure. *Pediatr Allergy Immunol* 1996; 17:495-500.
11. Gonzalo JA, Pan y, Lloyd CM *et al*. Mouse monocyte-derived chemokine is involved in airway hyperreactivity and lung inflammation. *J Immunol* 1999; 163:403-11.
12. Kawasasaki S, Takizawa H, Yoneyama H *et al*. Intervention of thymus and activation regulated chemokine attenuates the development of allergic airway inflammation and hyperresponsiveness in mice. *J Immunol* 2001; 166:2055-62.
13. Purandare AV, Wan H, Gao A *et al*. Optimization of CCR4 antagonists: Side-chain exploration. *Bioorg Med Chem Lett* 2006; 16:204-7.
14. Wang X, Xu F, Xu Q *et al*. Optimization of 2-aminthiazole derivatives as CCR4 antagonists. *Bioorg Med Chem Lett* 2006; 16:2800-3.
15. Yokoyama K, Ishikawa N, Igarashi S *et al*. Potent CCR4 antagonists: Synthesis, evaluation, and docking study of 2,4-diaminoquinazolines. *Bioorg Med Chem Lett* 2008; 16(17):7968-74.
16. Cascieri MA, Springer MS. The chemokine/chemokine-receptor family: potential and progress for therapeutic interventions. *Curr Opin Chem Biol* 2000; 4:420-7.
17. Horuk R, Clayberger C, Krensky AM *et al*. A non-peptide functional antagonist of the CCR1 chemokine receptor is effective in rat heart transplant rejection. *J Biol Chem* 2000; 275:25562-71.
18. Power CA, Proudfoot AE. The chemokine system: novel broad-spectrum therapeutic targets. *Curr Opin Pharmacol* 2001; 1:417-24.
19. Lagu B, Gerchak C, Pan M *et al*. Potent and selective CC-chemokine receptor-2 (CCR2) antagonists as a potential treatment for asthma. *Bioorg Med Chem Lett* 2007; 17:4382-6.
20. Hayworth B, Lin H, Fidock M, Dorr P, Strange PG. Allosteric effects of antagonists on signaling by the chemokine receptor CCR5. *Bio Pha* 2007; 74:891-7.
21. MacArthur RD, Novack RM. Reviews of anti-infective agents: maraviroc: the first of a new class of antiretroviral agent. *Clin Infect Dis* 2008; 47:236-41.
22. Rollins BJ. Chemokines. *Blood* 1997; 3:909-28.
23. O'Hayre M, Salanga CL, Handel TM, Allen SJ. Chemokines and cancer: migration, intracellular signalling and intercellular communication in the microenvironment. *Biochem J*. 2008;409:635-9.