

# Chemokine

**Overview:** Chemokine receptors (nomenclature agreed by NC-IUPHAR Subcommittee on Chemokine Receptors, Murphy *et al.*, 2000; Murphy, 2002) comprise a large subfamily of 7TM receptors activated by one or more of the chemokines, a large family of small cytokines typically possessing chemotactic activity for leukocytes.

Chemokines can be divided by structure into four subclasses by the number and arrangement of conserved cysteines. CC (also known as  $\beta$ -chemokines;  $n = 28$ ), CXC (also known as  $\alpha$ -chemokines;  $n = 16$ ) and CX<sub>3</sub>C ( $n = 1$ ) chemokines all have four conserved cysteines, with zero, one and three amino acids separating the first two cysteines respectively. C chemokines ( $n = 2$ ) have only the second and fourth cysteines found in other chemokines. Chemokines can also be classified by function into homeostatic and inflammatory subgroups. Most chemokine receptors are able to bind multiple high-affinity chemokine ligands, but the ligands for a given receptor are almost always restricted to the same structural subclass. Most chemokines bind to more than one receptor subtype. Receptors for inflammatory chemokines are typically highly promiscuous with regard to ligand specificity and may lack a selective endogenous ligand. Listed are those human agonists with EC<sub>50</sub> values <50 nM in either Ca<sup>2+</sup> flux or chemotaxis assays at human recombinant receptors expressed in mammalian cell lines. There can be substantial cross-species differences in the sequences of both chemokines and chemokine receptors, and in the pharmacology and biology of chemokine receptors. Endogenous and HIV-encoded non-chemokine ligands have also been identified for chemokine receptors. Many chemokine receptors function as HIV co-receptors, and at least two, CCR5 and CXCR4, play prominent roles in pathogenesis. The tables include both standard chemokine names (Zlotnik and Yoshie, 2000) and the most commonly used synonyms. Numerical data quoted are typically pK<sub>i</sub> or pIC<sub>50</sub> values from radioligand binding to heterologously expressed receptors.

| Nomenclature           | CCR1                                                                                                                            | CCR2                                                                              | CCR3                                                                                                                                                               | CCR4                                                      | CCR5                                                                                                                                       |
|------------------------|---------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|
| Other names            | CKR1, CC CK <sub>1</sub> , CC CKR1, MIP-1 $\alpha$ R, MIP-1 $\alpha$ /RANTES                                                    | CKR2, CC CK <sub>2</sub> , CC CKR2, MCP-1                                         | CKR3, CC CK <sub>3</sub> , CC CKR3                                                                                                                                 | CKR4, CC CK <sub>4</sub> , CC CKR4                        | CKR5, CC CK <sub>5</sub> , CC CKR <sub>5</sub> , CHEMR13                                                                                   |
| Ensembl ID             | ENSG00000163823                                                                                                                 | ENSG00000121807                                                                   | ENSG00000183625                                                                                                                                                    | ENSG00000183813                                           | ENSG00000160791                                                                                                                            |
| Principal transduction | G <sub>i/o</sub>                                                                                                                | G <sub>i/o</sub>                                                                  | G <sub>i/o</sub>                                                                                                                                                   | G <sub>i/o</sub>                                          | G <sub>i/o</sub>                                                                                                                           |
| Agonists               | CCL3 (MIP-1 $\alpha$ ), CCL5 (RANTES), CCL7 (MCP-3), CCL8 (MCP-2), CCL13 (MCP-4), CCL14a (HCC-1), CCL15 (HCC-2), CCL23 (MPIF-1) | CCL2 (MCP-1), CCL7 (MCP-3), CCL8 (MCP-2), CCL13 (MCP-4), CCL16 (HCC-4), HIV-1 Tat | CCL11 (eotaxin), CCL5 (RANTES), CCL7 (MCP-3), CCL8 (MCP-2), CCL13 (MCP-4), CCL15 (HCC-2), CCL24 (eotaxin-2), CCL26 (eotaxin-3), CCL28 (MEC), HIV-1 Tat             | CCL22 (MDC), CCL17 (TARC), HHV8 vMIP-III,                 | CCL3 (MIP-1 $\alpha$ ), CCL4 (MIP-1 $\beta$ ), CCL5 (RANTES), CCL8 (MCP-2), CCL11 (eotaxin), CCL14a (HCC-1), CCL16 (HCC-4), R5 HIV-1 gp120 |
| Selective agonists     | CCL15 (HCC-2), CCL23 (MPIF-1)                                                                                                   | CCL2 (MCP-1)                                                                      | CCL11 (eotaxin), CCL24 (eotaxin-2), CCL26 (eotaxin-3), Banyu Compound 1b (8.6), SB328437 (8.4), BMS Compound 87b (8.1), CXCL10 (IP10), CXCL9 (Mig), CXCL11 (I-TAC) | CCL22 (MDC), CCL17 (TARC)                                 | MIP-1 $\beta$ , R5-HIV gp120                                                                                                               |
| Selective antagonists  | BX471 (8.3-9), 2b-1 (8.7), UCB35625 (8.0), CP-481,715 (8.0), CCL4 (MIP-1 $\beta$ )                                              | CCL11 (eotaxin), CCL26 (eotaxin-3), GSK Compound 34 (7.6)                         | Compound 87b (8.1), CXCL10 (IP10), CXCL9 (Mig), CXCL11 (I-TAC)                                                                                                     | –                                                         | TAK779 (9.0), CCL7 (MCP-3), SCH C, SCH D, MRK-1, E913 (8.7), maraviroc, aplaviroc                                                          |
| Probes                 | [ <sup>125</sup> I]-MIP-1 $\alpha$ , [ <sup>125</sup> I]-RANTES, [ <sup>125</sup> I]-MCP-3                                      | [ <sup>125</sup> I]-MCP-1, [ <sup>125</sup> I]-MCP-3                              | [ <sup>125</sup> I]-RANTES, [ <sup>125</sup> I]-eotaxin, [ <sup>125</sup> I]-MCP-3                                                                                 | [ <sup>125</sup> I]-TARC, [ <sup>125</sup> I]-CTACK/CCL27 | [ <sup>125</sup> I]-RANTES, [ <sup>125</sup> I]-MCP-2, [ <sup>125</sup> I]-MIP-1 $\alpha$ , [ <sup>125</sup> I]-MIP-1 $\beta$              |

| Nomenclature           | CCR6                                               | CCR7                                             | CCR8                                                                          | CCR9                     | CCR10                                     |
|------------------------|----------------------------------------------------|--------------------------------------------------|-------------------------------------------------------------------------------|--------------------------|-------------------------------------------|
| Other names            | GPR-CY4, CKR-L3, STRL-22, DRY-6, DCR2, BN-1, GPR29 | EBI-1, BLR-2                                     | TER1, CKR-L1, GPR-CY6, ChemR1                                                 | GPR 9-6                  | GPR-2                                     |
| Ensembl ID             | ENSG00000153467                                    | ENSG00000126353                                  | ENSG00000179934                                                               | ENSG00000173585          | ENSG00000184451                           |
| Principal transduction | G <sub>i/o</sub>                                   | G <sub>i/o</sub>                                 | G <sub>i/o</sub>                                                              | G <sub>i/o</sub>         | G <sub>i/o</sub>                          |
| Agonists               | CCL20 (LARC), HBD2                                 | CCL19 (ELC, MIP-3 $\beta$ ), CCL21 (SLC)         | CCL1 (I-309), CCL4 (MIP-1 $\beta$ ), CCL16 (HCC-4), CCL17 (TARC), HHV8 vMIP-I | CCL25 (TECK)             | CCL27 (eskinine, ALP, CTACK), CCL28 (MEC) |
| Selective agonists     | LARC, HBD2                                         | ELC, SLC                                         | I-309                                                                         | TECK                     | Eskinine, MEC                             |
| Selective antagonists  | –                                                  | –                                                | MCV MC148R (vMCC-I)                                                           | –                        | –                                         |
| Probes                 | [ <sup>125</sup> I]-LARC                           | [ <sup>125</sup> I]-ELC, [ <sup>125</sup> I]-SLC | [ <sup>125</sup> I]-I309                                                      | [ <sup>125</sup> I]-TECK | –                                         |

| Nomenclature           | CXCR1                                                                   | CXCR2                                                                                                                                              | CXCR3                                                      | CXCR4                                                              | CXCR5               | CXCR6                      |
|------------------------|-------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------|--------------------------------------------------------------------|---------------------|----------------------------|
| Other names            | IL8R <sub>A</sub> , IL-8 receptor type I, IL-8 receptor $\alpha$        | IL8R <sub>B</sub> , IL-8 receptor type II, IL-8 receptor $\beta$                                                                                   | IP10/Mig R, GPR9                                           | HUMSTR, LESTR, fusin, HM89, LCR1                                   | BLR-1, MDR15        | STRL-33, BONZO, TYMSTR     |
| Ensembl ID             | ENSG00000163464                                                         | ENSG00000180871                                                                                                                                    | ENSG00000186810                                            | ENSG00000121966                                                    | ENSG00000160683     | ENSG00000172215            |
| Principal transduction | G <sub>i/o</sub>                                                        | G <sub>i/o</sub>                                                                                                                                   | G <sub>i/o</sub>                                           | G <sub>i/o</sub>                                                   | G <sub>i/o</sub>    | G <sub>i/o</sub>           |
| Agonists               | CXCL6 (GCP-2), CXCL8 (IL-8), cytokine domain of tyrosyl tRNA synthetase | CXCL1 (GRO $\alpha$ ), CXCL2 (GRO $\beta$ ), CXCL3 (GRO $\gamma$ ), CXCL5 (ENA78), CXCL6 (GCP-2), CXCL7 (NAP-2), CXCL8 (IL-8), HCMV UL146 (vCXCL1) | CXCL9 (Mig), CXCL10 (IP10), CXCL11 (I-TAC)                 | CXCL12 $\alpha$ (SDF-1 $\alpha$ ), CXCL12 $\beta$ (SDF-1 $\beta$ ) | CXCL13 (BLC, BCA-1) | CXCL16 (SR-PSOX)           |
| Selective agonists     | –                                                                       | GRO $\alpha$ , GRO $\gamma$ , GRO $\beta$ , NAP-2, ENA78                                                                                           | IP10, MIG, I-TAC                                           | SDF-1 $\alpha$ , SDF-1 $\beta$ , X4-HIV gp120                      | BLC                 | CXCL16                     |
| Selective antagonists  | –                                                                       | SB225002 (7.7)                                                                                                                                     | eotaxin, MCP-3                                             | AMD3100, HIV-1 Tat, T134, ALX41-4C                                 | –                   | –                          |
| Probes                 | [ <sup>125</sup> I]-IL8                                                 | [ <sup>125</sup> I]-IL8, [ <sup>125</sup> I]-GRO $\alpha$ , [ <sup>125</sup> I]-NAP-2, [ <sup>125</sup> I]-ENA78                                   | [ <sup>125</sup> I]-IP10, [ <sup>125</sup> I]-I-TAC/CXCL11 | [ <sup>125</sup> I]-SDF-1                                          | –                   | [ <sup>125</sup> I]-CXCL16 |

CXCR1 and CXCR2 also couple to phospholipase C when co-transfected with members of the G<sub>q/11</sub> family of G proteins. Mouse CXCR2 binds iodinated mouse KC and mouse MIP-2 with high affinity (mouse KC and MIP-2 are homologues of human GRO chemokines), but shows low affinity for human IL-8.

| Nomenclature           | CX <sub>3</sub> CR1             | XCR1                                                           |
|------------------------|---------------------------------|----------------------------------------------------------------|
| Other names            | CMKBR1, V28                     | GPR5                                                           |
| Ensembl ID             | ENSG00000168329                 | ENSG00000173578                                                |
| Principal transduction | G <sub>i/o</sub>                | G <sub>i/o</sub>                                               |
| Agonists               | CX3CL1 (Fractalkine)            | XCL1 $\alpha$ and $\beta$ (Lymphotactin $\alpha$ and $\beta$ ) |
| Selective agonists     | Fractalkine                     | Lymphotactin                                                   |
| Probes                 | [ <sup>125</sup> I]-Fractalkine | SEAP-XCL1                                                      |

Three human 7TM chemokine binding proteins have been identified that lack a known signalling function: D6 (ENSG00000144648), which binds multiple CC chemokines; a molecule previously inappropriately named CCR11 and now known as CCX CKR or the human homologue of the bovine gustatory receptor PPAR1 (ENSG00000118519, ENSG00000129048), which binds ELC, SLC and TECK; and Duffy, a highly promiscuous CC and CXC chemokine binding protein expressed mainly on erythrocytes. CXCR7 (former aliases: RDC1, CMKOR1 and GPR159, ENSG00000144476) binds CXCL11 and CXCL12 with high affinity, and is expressed in all four cardiac valves and by marginal zone B cells in mammals. Mice lacking this receptor undergo perinatal mortality because of valvular stenosis. Work in zebrafish has identified a role for a highly conserved CXCR7 homologue in shaping CXCL12 gradients, which guide primordial germ cell migration. Whether this is how it works in mammals, or whether there is, in addition, a signal transduction function for CXCR7 has not yet been fully resolved. Thus, the name CXCR7, though widely used in the field, has not yet been endorsed officially by IUPHAR. Specific chemokine receptors facilitate cell entry by microbes, such as *Plasmodium vivax*, HIV-1 and the poxvirus myxoma virus. Virally encoded chemokine receptors are known (e.g. US28, a homologue of CCR1 from human cytomegalovirus and ECRF3, a homologue of CXCR2 from *Herpesvirus saimiri*), but their role in viral life cycles is not established. Viruses can exploit or subvert the chemokine system by producing chemokine antagonists and scavengers.

The CC chemokine family (CCL1–28) includes I309 (CCL1), MCP-1 (CCL2), MIP-1 $\alpha$  (CCL3), MIP-1 $\beta$  (CCL4), RANTES (CCL5), MCP-3 (CCL7), MCP-2 (CCL8), eotaxin (CCL11), MCP-4 (CCL13), HCC-1 (CCL14), Lkn-1/HCC-2 (CCL15), TARC (CCL17), ELC (CCL19), LARC (CCL20), SLC (CCL21), MDC (CCL22), MPIF-1 (CCL23), eotaxin-2 (CCL24), TECK (CCL25), eotaxin (CCL26), eskine/CTACK (CCL27) and MEC (CCL28). The CXC chemokine family (CXCL1–16) includes GRO $\alpha$  (CXCL1), GRO $\beta$  (CXCL2), GRO $\gamma$  (CXCL3), platelet factor 4 (CXCL4), ENA78 (CXCL5), GCP-2 (CXCL6), NAP-2 (CXCL7), IL-8 (CXCL8), MIG (CXCL9), IP10 (CXCL10), I-TAC (CXCL11), SDF-1 (CXCL12), BLC (CXCL13), BRAK (CXCL14), mouse lungkine (CXCL15) and SR-PSOX (CXCL16). The CX<sub>3</sub>C chemokine (CX3CL1) is also known as fractalkine (neurotactin in the mouse). Like CXCL16, and unlike other chemokines, CX3CL1 is multimodular containing a chemokine domain, an elongated mucin-like stalk, a transmembrane domain and a cytoplasmic tail. Both plasma membrane-associated and shed forms have been identified. The C chemokine (XCL1) is also known as lymphotactin. The non-chemokine family includes the cytokine domain of tyrosyl-tRNA synthetase, HBD2, HIV gp120 and HIV Tat. Two chemokine receptor antagonists have now been approved by the FDA: the CCR5 antagonist maraviroc (Pfizer) for treatment of HIV/AIDS in patients with CCR5-using strains, and the CXCR4 antagonist AMD3100 (Plerixifor, Mozibil from Genzyme) for hematopoietic stem cell mobilization with G-CSF in patients undergoing transplantation in the context of chemotherapy for lymphoma and multiple myeloma.

**Abbreviations:** BLC, B-lymphocyte chemokine; ELC, Epstein–Barr virus-induced receptor ligand chemokine; ENA78, epithelial cell-derived neutrophil-activating factor-78 amino acids; GCP-2, granulocyte chemoattractant protein 2; HBD2, human  $\beta$  defensin 2; HCC, hemofiltrate CC chemokine; I-TAC, interferon-inducible T-cell  $\alpha$  chemoattractant; IL-8, interleukin 8; IP-10,  $\gamma$ -interferon-inducible protein 10; LARC, liver and activation-related chemokine (CCL20); MCP, monocyte chemoattractant protein; MDC, macrophage-derived chemokine; MEC, mucosa expressed chemokine; MIG, monokine-induced by  $\gamma$ -interferon; MIP, macrophage inflammatory protein; MPIF-1, myeloid progenitor inhibitory factor 1; NAP-2, neutrophil-activating peptide 2; RANTES, regulated on activation normal T cell expressed and secreted; SDF, stromal cell-derived factor; SEAP, secreted alkaline phosphatase; SLC, secondary lymphoid tissue chemokine; TARC, T-cell and activation-related chemokine; TECK, thymus-expressed chemokine

### Further Reading

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