Chemokines are small cytokines that control a wide variety of biological and pathological processes, from immunosurveillance to inflammation, and from viral infection to cancer. Genetic and pharmacological studies showed that chemokines are responsible for excessive recruitment of leukocytes to inflammatory sites and damaged tissue - thus prevention of this recruitment is an attractive anti-inflammatory therapeutic strategy. In this review we discuss the various entry points of intervention using either protein-based or small-molecule inhibitors; from receptor-ligand interaction, prevention of the chemokine-glycosaminoglycan interaction, interfering with the signaling pathways that are induced upon receptor activation.

As chemokines signal via seven-transmembrane G-protein-coupled receptors, which are favorite targets for the pharmaceutical industry, they are the first cytokines for which small-molecule receptor antagonists have been developed. Targeting chemokine intracellular signaling offers alternative small molecule interventions. For example, PI3Kδ deficient mice demonstrated impaired macrophage and neutrophil migration to inflammatory sites as well as defects in mast cell activation due to the specific disruption of chemokine mediated signaling at the level of PI3Kδ. Interestingly, similar phenotypes have been described for mice that lack certain members of Rho small GTPases. Thus the chemokine system offers many points of intervention for the development of innovative anti-inflammatory therapies for diseases, such as Multiple Sclerosis, Rheumatoid Arthritis and Allergic Contact dermatitis.