

Krohn SC, Bonvin P, Proudfoot AE. (2013). CCL18 exhibits a regulatory role through inhibition of receptor and glycosaminoglycan binding. *PLoS One*. Aug 12;8(8):e72321

CCL18 has been reported to be present constitutively at high levels in the circulation, and is further elevated during inflammatory diseases. Since it is a rather poor chemoattractant, we wondered if it may have a regulatory role. CCL18 has been reported to inhibit cellular recruitment mediated by CCR3, and we have shown that whilst it is a competitive functional antagonist as assessed by Schild plot analysis, it only binds to a subset of CCR3 receptor populations. We have extended this inhibitory activity to other receptors and have shown that CCL18 is able to inhibit CCR1, CCR2, CCR4 and CCR5 mediated chemotaxis, but has no effect on CCR7 and CCR9, nor the CXC receptors that we have tested. Whilst CCL18 is able to bind to CCR3, it does not bind to the other receptors that it inhibits. We therefore tested the hypothesis that it may displace glycosaminoglycan (GAG) chemokines bound either in cis- on the leukocyte, or in trans-presentation on the endothelial surface, thereby inhibiting the recruitment of leukocytes into the site of inflammation. We show that CCL18 selectively displaces heparin bound chemokines, and that chemokines from all four chemokine sub-classes displace cell bound CCL18. We propose that CCL18 has regulatory properties inhibiting chemokine function when GAG-mediated presentation plays a role in receptor activation.