But this still does not explain the activity of PGP, as it cannot mimic the ELR motif. I propose an alternate mechanism, in which the tripeptide binds to a site in the transmembrane region distinct from the chemokine binding sites, and subsequent conformational changes most probably parallel conformational changes that occur on chemokine binding, resulting in shared downstream signaling events. Most small-molecule agonists, including peptides, activate the GPCR receptor by binding to a site in the transmembrane helices[6]. One of the best studied is the tripeptide *N*-formyl-Met-Leu-Phe, and a variety of studies have shown that this peptide binds to a site in the transmembrane region[7]. Small-molecule inhibitors that target chemokine receptors including CXCR1 and CXCR2 receptors show no structural resemblance whatsoever to chemokines[8], so there is no reason to believe that the PGP tripeptide must mimic the chemokine structure for binding CXCR1 and CXCR2 receptors.

Krishna Rajarathnam

Department of Biochemistry and Molecular Biology, University of Texas Medical Branch, Galveston, Texas, 77555, USA.
E-mail: krrajara@utmb.edu

1. Weathington, N.M. *et al. Nat. Med.* **12**, 317–323 (2006).
2. Lee, Y.C. *et al. Biopolymers* **58**, 548–561 (2001).
3. Clark-Lewis, I., Dewald, B., Loetscher, M., Moser, B. & Baggiolini, M. *J. Biol. Chem.* **269,** 16075–16081 (1994).
4. Clark-Lewis, I., Dewald, B., Geiser, T., Moser, B. & Baggiolini, M. *Proc. Natl. Acad. Sci. USA* **90**, 3574–3577 (1993).
5. Rajarathnam, K., Dewald, B., Baggiolini, M., Sykes, B.D. & Clark-Lewis, I. *Biochemistry* **38**, 7653–7658 (1999).
6. Ji, T.H., Grossmann, M. & Ji, I. *J. Biol. Chem.* **273**, 17299–17302 (1998).
7. Meittinen, H.M. *et al. J. Immunol.* **159**, 4045–4054 (1997).
8. Bertini, R. *et al. Proc. Natl. Acad. Sci. USA* **101**, 11791–11796 (2004).

Weathington *et al.* reply:

We thank Krishna Rajarathnam for pointing out the two exceptions to the 'GP' rule. Our goal was to test the hypothesis that PGP acts as a specific neutrophil chemoattractant through an action on CXCR1, CXCR2 or both. We were pleased that he found the data supporting this hypothesis compelling. Our goal was not to ascertain the precise site of a PGP-receptor interaction. This will obviously require future structure-function studies, which may or may not support the mechanism suggested by Rajarathnam.

Nathaniel M Weathington[1], Anneke H van Houwelingen[2], Brett D Noerager[1], Patricia L Jackson[1], Aletta D Kraneveld[2], F Shawn Galin[1], Gert Folkerts[2], Frans P Nijkamp[2] & J Edwin Blalock[1]

[1]Department of Physiology and Biophysics, University of Alabama at Birmingham, 1918 University Boulevard, Birmingham, Alabama 35294, USA. [2]Utrecht Institute for Pharmaceutical Sciences, Department of Pharmacology and Pathophysiology, Utrecht University, Sorbonnelaan 16, 3584 CA Utrecht, The Netherlands.
E-mail: blalock@uab.edu