

*The GM-CSF Receptor - mechanisms for affinity conversion and signalling*

Sophie Elizabeth Broughton<sup>1</sup>, Timothy Hercus<sup>2</sup>, Tracy Nero<sup>1</sup>, Mara Dottore<sup>2</sup>, Barbara McClure<sup>2</sup>, Urmi Dhagat<sup>1</sup>, Houg Taing<sup>2</sup>, Michael Gorman<sup>1</sup>, Angel F Lopez<sup>2</sup>, Michael W Parker<sup>1,3</sup>

<sup>1</sup>ACRF Rational Drug Discovery Centre, St. Vincent's Institute Of Medical Research, Fitzroy, Australia, <sup>2</sup>The Centre for Cancer Biology, SA Pathology and the University of South Australia, Adelaide, Australia, <sup>3</sup>Department of Biochemistry and Molecular Biology, Bio21 Molecular Science and Biotechnology Institute, University of Melbourne, Victoria, Australia  
E-mail: sbroughton@svi.edu.au

The GM-CSF, IL-3, and IL-5 receptors constitute the beta c family, which regulate the production and function of cells within the haemopoietic and immune systems, and play important roles in inflammation, autoimmunity, and cancer [1]. Typical of heterodimeric type I cytokine receptors, signalling requires recruitment of the shared beta c subunit to the initial cytokine: alpha subunit binary complex through an affinity conversion mechanism [2]. This critical process is poorly understood due to the paucity of crystal structures of both binary and ternary receptor complexes for the same cytokine. We have now solved the structure of the binary GM-CSF:GMR-alpha complex at 2.8-Å resolution (PDB ID: 4RS1) and compared it with the structure of the ternary complex (PDB ID:4NKQ), revealing distinct conformational changes [3]. Guided by these differences we performed mutational and functional studies that, importantly, show GMR alpha interactions playing a major role in receptor signalling while beta c interactions control high affinity binding. These results support the notion that conformational changes underlie the mechanism of GM-CSF receptor activation and also suggest how related type I cytokine receptors signal.

[1] Broughton, S.E. et al (2012). Immunol Rev. 250, 277-302.

[2] Broughton, S.E. et al (2015). Cytokine, 74, 247-58

[3] Broughton, S.E. et al. (2016). Structure, 24, 1271-8.

**Keywords:** [GM-CSF receptor](#), [cytokine signalling](#), [receptor activation](#)