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# SEMINAR SERIES 2023
## 18 APRIL


## A/Prof Michael Griffin

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Associate Professor Griffin leads a laboratory in the Department of Biochemistry and Pharmacology at the Bio21 Molecular Science and Biotechnology Institute, the University of Melbourne. He completed his PhD at the University of Canterbury, New Zealand. In 2011 he was awarded an ARC Australian Postdoctoral Fellowship, in 2013 the C.R. Roper Fellowship and in 2015 an ARC Future Fellowship. A major research focus of his laboratory is on understanding the assembly and function of large, multimeric cytokine signalling complexes at the cell surface.

## Structures of the interleukin 11 signalling complex reveal dynamics of gp130 extracellular domains and a surprising inhibitory mechanism of a cytokine variant

Interleukin 11 (IL-11), an IL-6 family cytokine, plays pivotal roles in many autoimmune diseases, fibrotic complications, and solid cancers. IL-11 activates downstream signalling pathways by binding its two cell-surface receptors; the IL-11 specific receptor, IL-11Rα, and the shared IL-6 family signal-transducing receptor, glycoprotein 130 (gp130). Despite intense therapeutic targeting efforts, structural understanding of IL-11 signalling and mechanistic insights into current inhibitors remain limited. Here Associate Professor Griffin presents cryo-EM and crystal structures of the human IL-11 signalling complex, including the complex containing the complete extracellular domains of gp130. He shows that complex formation requires conformational reorganisation of IL-11, which is coordinated by a key arginine residue, R169 and also shows that the membrane-proximal domains of gp130 are dynamic and do not participate directly in signalling complex formation. He demonstrates that the cytokine mutant 'IL-11 Mutein' competitively inhibits IL-11 signalling in human cell lines. Structural shifts in IL-11 Mutein, caused by altered dynamics of a large loop region, underlie signalling inhibition. These structural alterations modulate cytokine binding interactions at all three receptor-engaging sites of the cytokine, including abrogating the final gp130 binding step. The results reveal the structural basis of IL-11 signalling, define the molecular mechanisms of an inhibitor, and advance understanding of receptor dynamics in gp130-containing receptor complexes. These insights provide invaluable molecular platforms for development of existing and novel therapeutics targeting IL-11 signalling and signalling by other class I cytokines.