

**P016** Modelling TLR4 TIR Receptor:Adaptor Interactions – A Specific Scaffold for Adaptor Recruitment  
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Activation of Toll-like receptor 4 (TLR4) is believed to be through ligand induced dimerisation. This results in conformational change in the receptor leading to homodimerisation of the intracellular Toll/Interleukin 1 receptor (TIR) signalling domain. This generates a new protein scaffold for the recruitment of the downstream signalling adaptors; Mal and MyD88, and TRAM and TRIF.

We have recently generated high quality models of the TLR4 TIR homodimer, the TIR domains of the adaptor proteins Mal and TRAM, and complexes of TLR4 with both Mal and TRAM. Remarkably both Mal and TRAM are strongly predicted to bind at two symmetry-related sites on the homodimer interface. The proposed model is consistent with extensive functional studies, both of our own and those published in the literature. These include phenotypic characteristics of TLR4 and Mal mutants, the impact of site directed mutagenesis on receptor signalling, the effect of stable protein phosphorylation, and the inhibition of receptor activation by cell permeable peptides specific to the BB loops of the receptor and adaptors.