

**P006** Involvement of Fc $\gamma$ RII signalling in the neutralization of LPS activity via a potent novel anti-TLR4 MAb  
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LPS from Gram-negative bacteria activates TLR4 and induces a signalling cascade that, when exaggerated, has been causally associated with severe sepsis. We have generated an anti-human TLR4 MAb, 15C1 (mouse IgG1), which potently blocks the effects of LPS on a panel of primary cells and cell lines *in vitro* and in a whole blood assay *ex vivo*. The binding of 15C1 was mapped to an epitope in the second portion of the extracellular region of TLR4, which has previously been shown to be functionally important in the recognition of LPS. Furthermore, we demonstrate that the mechanism of inhibition of 15C1 is partially dependent on the mouse IgG1 Fc portion of the MAb, and involves the Fc $\gamma$  II receptor CD32A. A humanized (human IgG1) version of 15C1 (hz15C1) generated by CDR grafting retained affinity for TLR4 but demonstrated a significant loss in its ability to inhibit LPS activity. Potency could be completely regained by restoring CD32A interaction via the replacement of 3 amino acids within the CH2 domain of human IgG1 with the corresponding residues from mouse IgG1. We propose this modified version of hz15C1 as a potent therapeutic agent in diseases involving stimulation of TLR4.