P038 Inhibition of TLRs in Rheumatoid Arthritis (RA) reduces inflammation in the murine CIA model and inflammatory cytokines in the human RA model

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Rheumatoid arthritis (RA) is a debilitating auto-immune condition that affects the joints and occurs in approximately 1% of the world's population. We have recently demonstrated a role for TLR adaptor proteins MyD88 and Mal in inflammatory cytokine production from human RA synovial membrane cell cultures. Further studies to evaluate which TLRs were functional in these mixed cell cultures indicated that activation of all TLRs except TLR7 and 9 were able to increase the amount of TNF released. We went on to identify inhibitors which decrease cytokine production from TLR activation. Studies using these inhibitors in the CIA murine model of RA showed a significant inhibition of both the histology scoring and clinical score in the groups treated with the inhibitors. Human studies using the RA synovial membrane cell culture model revealed significant inhibition in the spontaneous production of TNF, IL-1 and IL-6 production in the presence of these inhibitors. These cytokines are all validated therapeutic target for the treatment of RA.