The effect of *Mycobacterium obuense* on Dendritic Cells and the adaptive immune response

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Background
IMM-101 is an immunomodulatory treatment, comprising of heat killed whole cell *Mycobacterium obuense* (NCTC13365), currently under clinical investigation in pancreatic cancer. The need for new treatment options is highlighted by the median overall survival being only 6-12 months with current therapies. IMM-101 treatment in parallel with the first line therapy Gemcitabine increases median survival to 7.0 months in patients with metastatic pancreatic cancer, compared to 4.4 months following treatment with Gemcitabine alone (Dalgleish et al., *BJC*, 2016).

Aim
To understand the impact of IMM-101 on the innate and adaptive immune response.

Methods
Dendritic cell (DC) studies were conducted using GM-CSF derived murine DCs (GMDCs) or human monocyte derived DCs. DC phenotypic activation was assessed via flow cytometry and cytokine secretion assessed by ELISA. Co-culture studies were carried out using GMDCs and CFSE labelled T cells isolated from transgenic OTII mice. Additionally, WT, IL-12p40$^{-/-}$ or IL-12p35$^{-/-}$ GMDCs were adoptively transferred into in either SPF or Germ Free (GF) C57BL/6 mice.

Results
Initial work identified a dose dependent impact of IMM-101 on the activation of both human and murine DCs, with an increase in activation markers (CD40, CD80 and CD86) and cytokine production (IL-6, IL-12p40 and NO). Adoptive transfer of IMM-101 activated DCs instigated an IFN-γ and IL-17 response *in vivo*, with a cross-reactive response evident against other bacterial antigens. Interestingly, initial data suggest that the IMM-101 DC induced IFN-γ response may be independent of DC IL-12 production. Work in GF models has suggested that the effects of IMM-101 are unlikely to be a result of commensal bacterial involvement.

Conclusion
Our demonstration that IMM-101 activates murine and human primary DCs, as well as promoting IFN-γ and IL-17 production *in vivo* helps us to elucidate the fundamental mechanisms behind this promising cancer treatment.