**BRITSpA ABSTRACT COMPETITION WINNER 2018**

**An Entheseal Innate Immune Cell Biological basis for differential efficacy of PDE4 and IL-23 pathway blockade between Psoriatic Disease and Rheumatoid Arthritis**

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**Introduction**

Both IL-23 and PDE4 inhibition are ineffective in RA but show efficacy in PsA related synovitis despite similar cytokine and molecular profiles between synovitis in both disease settings. We hypothesised that enthesis resident innate immune cells, especially myeloid cells, might be capable of IL-23 production that could be modulated by PDE4 pathway blockade.

**Materials and Methods**

Human entheses (n=6) were digested and myeloid cells (CD14+) sorted from both the adjacent bone (EB) and soft tissue (ST) fractions. Both CD14+ sorted and CD14- unsorted cells were stimulated with bacterial and fungal adjuvants (TLR and CLR agonists) in the presence and absence of a PDE4 inhibitor and analysed by ELISA and flow cytometry for production of disease relevant mediators (IL-23, TNFα, and CCL20). Corresponding peripheral blood populations were also stimulated with and without a PDE4 inhibitor and other cAMP elevating agents to confirm the role of cAMP in regulating IL-23 associated inflammation.

**Results**

A CD45+/HLADR+/CD14+ myeloid cell population could be isolated from the normal enthesis in both the ST and EB fractions but with a much higher abundance in EB. This purified population from both ST and EB produced IL-23, TNFα and CCL20 following TLR/CLR receptor stimulation. IL-23 and TNFα production wasnegligible in the CD14- fraction. Moreover, IL-23 and TNF induction was inhibited by the PDE4 inhibitor rolipram. In blood derived myeloid cells, rolipram and other cAMPelevating agents (histamine and 8-br-cAMP), also inhibited IL-23 secretion**.**

**Conclusion**

These findings demonstrate that the human enthesis harbours an IL-23 producing myeloid cell population which can be modulated by PDE4 pathway manipulation. These findings support the idea of the IL-23/17 pathway genetic architecture of SpA in the context of entheseal biologyand offer a “reverse translation” explanation for divergent therapeutic pathways between SpA and RA.

