TRAM (Train and Retain Academic Musculoskeletal clinicians)
MB-PhD Project Summary

PhD project Title
How does intestinal inflammation contribute to systemic inflammation in seronegative arthritis?

PhD supervisors (please provide name, affiliation and email) *[At least two supervisors]*	
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Background
Antibodies play crucial pathogenic roles in seropositive arthritis. However, clinical, genetic and experimental evidence from patients, and data from animal models, all support the hypothesis that intestinal inflammation contributes to the pathogenesis of seronegative inflammatory conditions. With the Bowness group, we have previously demonstrated, for instance, that in patients with spondyloarthritis (SpA) expression of the intestine-homing chemokine receptor CCR9 on circulating T cells positively correlates with levels of systemic inflammation (Wright et al., 2016). The Bowness lab in Oxford have also recently described immune-mediated interactions with the intestine that contribute to SpA pathogenesis (reviewed in Simone, Mossawi, & Bowness, 2018). Expression of the MHC class I molecule HLA-B27 is very strongly associated with SpA. Here we will use samples from HLA-B27 positive individuals, and from SpA patients, to test hypotheses relating intestinal inflammation to peripheral symptoms of seronegative arthritis.

Aim
Using samples from patients with seronegative inflammatory arthritis, to investigate the cellular and molecular mechanisms connecting the intestine and systemic inflammatory pathology.

Training and experience provided *[Include types of methodologies that will be employed]*
This project has three related goals. The first is to investigate whether cell populations associated with intestinal inflammation are present in blood samples from patients with SpA. A number of characteristic, intestinally-activated circulating immune cell populations have recently been identified in patients with inflammatory bowel disease (IBD), and in animal models, including specific T cell and monocytic populations. We predict that multi-parameter flow cytometric analysis of blood samples from people with SpA will reveal characteristic immune-phenotypic changes consistent with those we, and others, have recently observed in patients with inflammatory bowel disease (manuscript submitted). Specifically, we will investigate whether the intestinally-activated T cell and monocytic populations identified in people with IBD are present in blood from people with SpA. The second goal is to directly assess intestinal inflammation using colonic and ileal biopsies obtained from HLA-B27-positive patients who attend for routine colonoscopy. Through our ongoing collaborations with Drs Gaya (Glasgow Royal Infirmary), MacDonald, and Seenan (Gartnavel General Hospital) we have access to large numbers of biopsies, obtained with consent for research, and stored with the NHS GG&C Biorepository and Glasgow Research Tissue Biobank. We predict that expression of HLA-B27 will cause measurable histological

changes in the tissue, consistent with low levels of inflammation. Changes to the intestinal epithelial barrier have been previously reported in people with SpA (Ciccia et al., 2017), and animal models suggest a key role for HLA-B27 modulating this through interactions with the microbiota. The mechanisms underlying this have not yet been elucidated in humans, therefore we will begin by investigating alterations in epithelial barrier function and in the functions of goblet cells, using a range of microscopic imaging modalities (e.g. immunohistochemistry, RNAscope, confocal fluorescent microscopy)

Our third goal is to investigate the cell populations found within the intestine of people with SpA and how these correlate with cell populations in blood. To achieve this, we will co-ordinate between the gastroenterologists and our colleagues in Rheumatology, Drs McCarey, McEntegert (Glasgow Royal Infirmary) and Reid (Gartnavel General Hospital), to obtain colon biopsies from the small number of SpA patients who attend for colonoscopy. Matched blood samples will also be obtained from these patients, and both will be analysed by single cell sequencing. We hypothesize that specific cell populations involved in inflammatory pathogenesis (comparison with available public datasets), for example, those seen in inflammatory bowel disease, will be present within both the intestine and the blood, indicating shared immune mechanisms.

Expected outcomes

The ultimate goal is to better understand the cellular and molecular immune mechanisms driving intestinal inflammation in SpA. Understanding the importance of intestinal inflammation in seronegative arthritis could enable identification of prognostic biomarkers and inform treatment strategies.

References

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