Project Details	
Project Code	MRC22IIARBr Jones
Title	Identifying new therapeutic targets and testing their potential for the treatment of chronic inflammation in arthritis.
Research Theme	Infection, Immunity, Antimicrobial Resistance & Repair
Summary	Drugs that block cytokine activity have revolutionised the treatment of rheumatoid arthritis. However, the ~40% of patients who develop ectopic lymphoid-like structures (ELS) within inflamed joints continue to display severe disease and an inadequate response to these current drugs. The PhD student will use in vivo arthritis models, imaging and cutting-edge next-generation sequencing methods to find new ways of targeting ELS to support precision medicine.
Description	IMPORTANCE Rheumatoid arthritis is a complex disease where patients present with distinct forms of joint inflammation (synovitis) that influences disease progression. The 'lymphoid-rich' form of synovitis (~40% of patients) features organised clusters of immune cells called ectopic lymphoid structures (ELS). ELS drive local immune cell priming and disease-specific autoantibody generation (e.g. rheumatoid factor). Thus, patients with synovial ELS display severe disease and an inferior response to frontline biological drugs (e.g. anti-TNF). Investigating ELS is critical to understand their role in disease and to find ways of targeting them therapeutically. Our research shows that control of CD4 T cells by IL-6 family cytokines (e.g. IL-6, IL-27) is a critical checkpoint in the development of ELS. However, the mechanisms by which CD4 T cells regulate ELS activity remain ill-defined. Combining whole-tissue transcriptomic analysis with immunodetection methods, we have identified cytokine networks and transcriptional programmes involved in ELS regulation in experimental and clinical arthritis. Significantly, our research shows that these cytokines are also integral to ELS formation in cancer and infection, thus revealing important cross-disease effector mechanisms that regulate ELS. We hypothesise that cytokine networks that govern CD4 T cell responses control synovial ELS development and represent modifiable therapeutic targets for the treatment of patients with ELS-rich arthritis. This project aims to provide mechanistic insight into ELS regulation in arthritis with broad-reaching relevance to other conditions where ELS influence disease progression in autoimmunity, infection and cancer. RESEARCH TRAINING Aim 1. Identify cellular mechanisms underpinning CD4 T cell control of ELS in arthritis Building on our whole-tissue transcriptomic analysis, the student will become expert in in vivo models of arthritis and use next-generation sequencing (NGS) methods (RNA-sequencing, ATAC-sequencing) to identify CD4 T cell mechanisms that promote ELS pathology. Joint-infiltrating CD4 T cells will be recovered from mice with synovial ELS and compared to systemic naïve and effector CD4 T cells to identify joint-specific effector functions linked to ELS development and maintenance. Aim 2. Test the clinical significance of T cell signatures linked with ELS pathology Gene signatures from Aim 1 will be validated against transcriptomic datasets of early rheumatoid arthritis (e.g. ArrayExpress E-MTAB-6141, dbGaP phs001457.v1.p1) to confirm their clinical significance in lymphoid-rich disease. Gene programmes linked with synovial ELS control will also be compared to available datasets from cancers featuring tumour-

	associated ELS (The Cancer Genome Atlas) to identify potential cross-disease mechanisms by which CD4 T cells regulate ELS. Aim 3. Testing therapeutic targets and imaging of synovial ELS Targeting of ELS will be based on pathways identified in Aims 1-2 and targets of interest linked to T helper (Th)17, T follicular helper (Tfh) and T cell-neutrophil crosstalk. Histopathology, immunofluorescence and flow cytometry will track synovial T cell responses and ELS development in vivo. Light Sheet fluorescent microscopy will, for the first time, provide a cutting-edge 3D spatial characterisation of ELS in our model. ADDED VALUE The student will benefit from collaboration and interaction with clinical (Costantino Pitzalis, William Harvey Research Institute) and industrial (e.g. GlaxoSmithKline) collaborators where the project will also inform parallel studies. KNOWLEDGE TRANSFER AND IMPACT The student will communicate research through peer-reviewed publications and presentations at internal, GW4, national and international scientific meetings. Engagement with our patient insight partner will ensure the research addresses the unmet needs of patients and is communicated publicly through engagement events and the media.
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