Project Details	
Project Code	MRC23IIARBr JonesG
Title	Identifying immune mechanisms and testing new therapeutic targets for inflammatory arthritis and associated comorbidities
Research Theme	Infection, Immunity, Antimicrobial Resistance and Repair
Summary	Cytokine-blocking drugs have revolutionised the treatment of inflammatory arthritis. However, ~40% of patients show poor responses to these drugs, continue to display severe disease and also suffer comorbidities (e.g. cardiovascular disease, uveitis). The student will use in vivo arthritis models, imaging, and bioinformatics to test the therapeutic potential of targeting coexisting immune mechanisms active in arthritic joints and tissues affected by comorbidity.
Description	IMPORTANCE The incidence of autoimmune and immune-mediated inflammatory diseases (IMIDs) is increasing. These diseases often coexist with chronic conditions that cause disability and mortality. Consequently, multimorbidity is forecast as an upcoming global health challenge. Research into conditions that coexist is nearly always performed separately, hampering the discovery of shared mechanisms that link systemic immune dysregulation with concurrent damage to different tissues. This project aims to increase our understanding of concurrent immune mechanisms active in tissues primarily affected by IMIDs and sites of co-/multi-morbidity. Such insight has the potential to inform the design of improved interventions for patients with IMIDs and complex comorbidities. Patients with inflammatory arthritis are at higher risk of cardiovascular (CV) disease. Strong evidence points to systemic inflammation in driving this risk. Uveitis and arthritis also coexist in patients with spondyloarthropathies and juvenile idiopathic arthritis. To gain new perspective on tissue events underpinning comorbidities, our studies combine an evaluation of inflamed joints in arthritis, with coexisting immune and functional changes in CV tissues and eyes. Our research reveals that control of CD4 T cells by IL-6 family cytokines critically determines arthritis progression, but also immune cell recruitment to CV tissue and eyes. Combining RNA-sequencing with immunodetection methods, we have identified cytokine networks and T cell effector programmes that coexist across the arthritic joint, CV and ocular tissues. We propose that targeting these pathways has therapeutic application for arthritis-associated CV disease and uveitis. Significantly, drugs against some of these targets show good safety in recent clinical trials (e.g. in cancer) highlighting their potential for repurposing. RESEARCH TRAINING Aim 1. Identify coexisting immune mechanisms in CV and ocular tissue during experimental arthritis. Training in bioinformatics, pathway analysis and data visualisation using our recent RNA-sequencing datasets will enable the student to choose tractable immune targets of interest to them. They will use models of arthritis, in vivo imaging (optical coherence tomography) and immunodetection (immunohistochemistry, Light sheet and fluorescence microscopy, flow cytometry) to validate and spatially localise mechanisms of immune activation in CV tissues and eyes because of arthritis. Aim 2. Targeting effector functions that determine CD4 T cell pathogenicity. Human and mouse CD4 T cell cultures will determine how targets from Aim 1 are regulated in T cells and how inhibition (e.g.

	antibody blockade, small molecule inhibitors, gene knockdown) alters their function and pathogenicity. The student will track effects including proliferation, function (cytokine secretion, activation markers) and cellular metabolism (Agilent Seahorse, with Dr N. Jones, Swansea University). Aim 3. Testing the impact of target inhibition on arthritis-associated comorbidities. Arthritis will be induced in mice and the effect of target inhibition on arthritis severity, and co-existing CV and ocular inflammation, will be determined by clinical assessments, imaging, histopathology and measuring vascular function (with Prof A. Williams, Cardiff University). ADDED VALUE The student will benefit from collaboration with clinical rheumatologists and ophthalmologists (Profs Ramanan and Dick, Bristol Medical School), academics (Dr N. Jones, Prof Williams) and industry (e.g. GlaxoSmithKline) where the project will 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 unmet patient needs and is effectively communicated through engagement events.
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