Project Details	
Project Code	MRC23IIARBa Thompson
Title	TARGETING ADIPOSE-DERIVED ADIPSIN FOR THE TREATMENT OF ARTHRITIS
Research Theme	Infection, Immunity, Antimicrobial Resistance and Repair
Summary	Adipose tissue is much more than an energy store. Recent evidence from rodent models indicates that a major product of adipose tissue (adipsin) plays a direct role in the pathogenesis of immune mediated inflammatory arthritis. This interdisciplinary project will determine the role of adipsin in humans, including whether targeting adipsin has the potential to prevent and/or treat inflammatory arthritis and osteoarthritis.
Description	BACKGROUND: Recent studies using genetically modified (knock-out) mouse models demonstrate that adipose-derived adipsin (Complement Factor D) drives the aetiology and progression of both inflammatory arthritis (PMID: 31167128) and knee osteoarthritis (PMID: 32012117). Cross-sectional human studies indicate that elevated adipsin is associated with age-related inflammatory conditions such as macular degeneration, atherosclerosis, and cognitive impairment. We recently showed that adipose tissue displays profound pro-inflammatory transcriptomic changes and ~2-fold more immune cells per gram with ageing in humans, and this was associated with both increased adipsin secretion from adipose tissue explants, and elevated circulating adipsin concentrations (PMID: 33895996). Based on these prior observations, we hypothesise that adipose tissue inflammation leads to aberrant (raised) adipsin secretion and circulating concentrations, and that this influences the pathogenesis of inflammatory arthritis and osteoarthritis in humans. PROJECT OVERVIEW AND KEY QUESTIONS: The overarching aim of this project is to examine the role of adipsin in inflammatory arthritis and osteoarthritis, and to determine whether it is possible to either manipulate the secretion of adipsin, and/or block adipsin action. The initial phases of the project will capitalise on samples already available across the project partners. The Royal National Hospital for Rheumatic Diseases (RNHRD) has a biobank of blood samples from (~1000) patients with different forms of inflammatory arthritis (e.g., rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis), as well as a much larger bank of clinical and individual-level patient data (>30,000). Targeted analysis of selected blood samples from this biobank will provide data to model the relationship between adipsin and different forms of inflammatory arthritis in humans for the first time. In parallel, the student will be able to access synovial fluid and biopsies from mouse models of rheumatoid arthritis provided by Cardiff, as well as associated transcriptomics data from RNA sequencing, to characterise and examine adipsin-related pathways in the inflamed joint. Subsequent experimental work will be shaped by the student, depending on their scientific and/or training-related preferences, and underpinned by findings from the above earlier studies. We see an opportunity to examine the cellular source of adipsin in specific groups of people (e.g., to examine ex vivo secretion/expression in the different cells that make up adipose tissue, including adipocytes, immune cells, and preadipocytes), and to examine the link between adipose tissue inflammation, adipsin secretion and

	disease activity. Adipose tissue explants can be cultured to examine whether adipsin secretion can be normalised or manipulated ex vivo – or whether the downstream action of adipsin can be inhibited. In addition, it would be possible to examine changes in adipsin secretion in patient populations receiving treatments that are likely to exert effects on adipose tissue inflammation, such as anti-TNF therapies. Alternatively, there would also be the opportunity to characterise adipsin secretion in vivo (e.g., studies of diurnal rhythm, effects of feeding and so on), or to develop/test non-pharmacological interventions that could be used to target adipose tissue in specific patient populations (e.g., exercise, weight loss, omega-3 supplementation). TRAINING FOR THE STUDENT: This project is an excellent training opportunity. This includes technical training, such as the use of flow cytometry, qPCR, western blotting, and cell culture – plus the development of bioinformatics skills using curated datasets. There is also the opportunity to develop skills in the conduct of human studies, ranging from working with existing patient samples and datasets through to the development and implementation of new human intervention studies.
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