Scientific summary

Ankylosing Spondylitis (AS) is a form of chronic inflammatory arthritis of the spine and peripheral joints. It is closely related to other spondyloarthopathies (SpA), such as reactive arthritis triggered by bacterial infections and arthritis associated with inflammatory bowel disease (IBD). IL-23 dependent spondylitis, arthritis and ileitis recapitulate human SpA in curdlan-treated SKG mice. SpA patients and SKG mice have fecal dysbiosis with increased gram-negative bacteria. In SKG mice, anti-IL-23 treatment supports homeostatic bacteria, gut integrity and is sufficient to prevent arthritis. In this project, germ-free (GF) SKG or control BALB/c mice were colonised for 4 weeks with *Parabacteroides* sp. (Para), *Lactobacillus murinus* (Lm), or altered Schaedler flora (ASF) comprising *Para*, *Lm*, *Mucispirillum Schaedleri*, and *Clostridium* sp., then given curdlan. We assessed gene transcripts, goblet cells and bacterial DNA in small intestine (ileum) and in the inflamed joints (rear paw). *Para* or Lm monocolonised SKG mice, but not GF mice or BALB/c mice, developed IL-23-dependent ileitis and arthritis within five weeks post-curdlan. One week post-curdlan, in the ileum, stress-related *Il23a*, *Grp78* and *sXbp1* gene expression was significantly increased, and the number and tight junctions of mucin-producing goblet cells were compromised, confirming reduced gut barrier integrity. Concomitantly, *Para* or Lm translocated from gut lumen to the villi where macrophages and neutrophils captured them. Bacterial DNA was found within macrophages and neutrophils in inflamed joints. In contrast, SKG colonised with ASF were protected from ileitis but not arthritis, with enhanced regulatory mechanisms in the gut. Overall, we showed that gut-derived bacteria are a key player in the development of arthritis. This opens exciting new opportunities to treat the cause of the disease rather than the symptoms, by developing curative strategies to enhance gut health and control harmful bacteria.

How gut bacteria in the joint activate arthritogenic inflammation is still unknown. This is the subject of ongoing work in Prof. Thomas laboratory. Recently, expanded $CD8^+$ T cell clones were identified by a UK team in blood, joints and eye of multiple AS patients. The clones recognised peptides derived from gut bacteria and self-antigens presented by HLA-B27. Our laboratory is examining expanded $CD8^+$ T cell clonotypes in gut and synovial tissue of HLA-$B27^+$ AS patients with arthritis with and without ileal inflammation to understand which T cells are pathogenic in AS, what they recognise, where they migrate, how they signal and how they differ during active disease, remission and the healthy state. Ultimately we aim to understand disease-relevant antigens in order to develop antigen-specific immunotherapy for SpA.