Project Details	
Project Code	MRC22IIARCa Eberl
Title	Control of mucosal immunity and intestinal integrity by human gamma/delta T cells
Research Theme	Infection, Immunity, Antimicrobial Resistance & Repair
Summary	γδ T cells are 'unconventional' lymphocytes that promote mucosal barrier defence and regulate immune responses to microbial infection. This PhD will use gene expression profiling, functional studies on cells from human blood and intestine, and organ chip-based / in vivo models to define how microbe-responsive γδ T cells control CD4+ T cell immunity and intestinal barrier function in health and inflammation.
Description	Background and significance. Human 'unconventional' lymphocytes are increasingly recognised to sense pathogens, influence recruitment and function of other immune cells, and help protect body tissues against infection. This project will study how γδ T cells in human blood and intestine control 'conventional' CD4+ T cell responses in health and disease. Polarisation of CD4+ T helper cells into Th1, Th2, Th17 and Treg cells is crucial for host defence against pathogens and tumours, but also for wound healing and resolution of inflammation. Better understanding of this process will therefore help inform the development of novel vaccines, treatments and diagnostics for a range of pathologies. Preliminary work. Our data demonstrate a striking plasticity of human γδ T cells to modulate immunity at epithelial sites. A previous PhD student already identified γδ T cell signals that drive expression of the tissue-protective factors IL-22 and calprotectin in the human intestine (Tyler et al., 2017). More recent work shows that human γδ T cells can also induce anti-inflammatory CD4+ T cell responses marked by the expression of IL-10 (Eberl and McCarthy, unpublished). Objective. To define the molecular mechanisms underlying CD4+ T cell polarisation by human γδ T cells during homeostasis and infection, and to identify ways to manipulate relevant pathways for future interventions Aim 1. [Eberl, McCarthy] To study the potential of human γδ T cells to polarise primary CD4+ T cells towards distinct T helper subsets (Th1, Th2, Th17, Th22, Tfh, Treg). Aim 2. [Eberl, Jones, McCarthy] To define the molecular signals that polarise CD4+ T cells towards distinct effector subsets by RNAseq profiling of activated human γδ T cells. Aim 3. [McCarthy, Eberl] To validate polarising signals and manipulate pathways in cell culture, human intestinal tissues and gut-on-a-chip systems. Aim 4. [Jones, Eberl] To investigate polarising pathways in mouse models: in vitro/in vivo T cell polarisation by signals identified in Aims 2+3 (with focus on CD4+ T-cells producing IL-10 or IL-22, and signalling via ICOS/ICOSL and CD30/CD30L). Research Training. The student will receive expert training in core immunological techniques (cell culture, flow cytometry, cell sorting, ELISA, qPCR), organ-on-a-chip approaches, animal husbandry, gene profiling strategies (RNA sequencing) and bioinformatical analyses (Ingenuity Pathway Analysis). Added-value. The student will work across disciplinary boundaries, by combining functional studies, bioinformatics approaches, analyses of clinical biopsies, organ chip systems, and in vivo models of inflammation. The student will take advantage of an established collaboration between Eberl and McCarthy, and benefit from extensive clinical expertise at The

	Blizard Institute at QMUL and cutting edge in vivo models at the University of Bristol. Knowledge transfer and impact. The student will communicate their research to specialist and lay audiences through publications and presentations, and via engagement and outreach activities. Protocols and data will be freely exchanged between the three collaborating groups. Clinical implications of the findings will be discussed with the clinical team at Barts NHS Trust and with the Technology Transfer Office at Cardiff University.
Supervisory Team	
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