Project Details	
Project Code	MRCIIAR24Ca Ladell
Title	Clonal aging of anti-viral T cells impacts protective immunity
Research Theme	Infection, Immunity, Antimicrobial Resistance & Repair
Summary	The induction and persistence of effective antigen(Ag)-specific memory T-cell responses is required to bestow long-term protection against infectious diseases, and hence is critical to vaccine development. However, evolution of such T-cell responses can lead to impaired secondary (e.g. to influenza virus) or aberrant (e.g. to Dengue virus) responses. The student will examine age and evolution of several Ag-specific T-cells responses at steady state and over time.
Description	Significance The fundamental basis of T-cell memory remains elusive. It is established that antigen stimulation drives clonal proliferation and differentiation, but the relationship between clonal composition and replicative history, and longevity, which is likely essential for durable memory, has proven difficult to elucidate. Furthermore, the ability of the immune system to protect humans from infection wanes during adult age. As a consequence, the risk of suffering more severe symptoms or even death when infected with novel or altered microbial pathogens (e.g. bacteria, parasites, and viruses) is greater in older than in younger adults, as highlighted by the recent emergence of pandemic and variant strains of the coronavirus SARS-CoV-2. We are in a position to advance our understanding of T-cell persistence and ageing by combining multi-parameter flow sorting, including single cell index sorting, using fluorescent peptide-loaded Human Leukocyte Antigen (pHLA) tetramers either un-mutated or mutated at the CD8 binding site for the identification of Ag-specific cells with higher and lower avidity T-cell receptors (TCRs), Single telomere length analysis (STELA) and single cell TCR sequencing. The new knowledge revealed by the proposed studies will uncover determinants of T-cell persistence and ageing, and will improve our understanding of protective cellular immunological memory. Originality 'Memory' T cells, which have already proliferated and matured in response to previous encounters with microbial pathogens, can persist for a long time in the body, either by remaining dormant and/or by cell division. The problem is that T cells cannot divide a limitless number of times, because structures known as telomeres, which essentially count the number of cell divisions, shorten progressively until they become too short to support further cell proliferation. This process of telomere shortening can now be measured accurately using a highly sensitive technique developed in Cardiff, namely 'Single-Telomere Length Analysis' or STELA. STELA can be used to reliably determine telomere lengths of Ag-specific cells not only because it assesses telomere length at a single chromosome, but also, as it is a molecular technique downstream of cell identification, i.e. it does not alter cell surface characteristics. Research Question A number of factors influence the clonal composition during acute infection and over time of Ag-specific T cell responses with key players being the antigen presenting machinery, i.e. the HLA, the antigen (Ag) being presented and the TCRs present in the precursor pool. A key question that remains is whether immune aging involves loss of Ag-specific clones from Ag-specific responses due to accelerated kinetics related to the

	strength/avidity of the TCR-Ag interaction. Objectives The PhD student will - Examine aging of human Ag-specific T-cells specific for Ags from different viruses* directly ex vivo. *Dominant and subdominant Ag-specific responses to Cytomegalovirus(CMV), Dengue, influenza, Epstein-Barr Virus (EBV), SARS-CoV-2, Yellow Fever Virus (YFV). - Determine the clonal composition of Ag-specific T-cell responses to allow reliable sorting of T-cells with high and low avidity TCRs. - Determine how TCR avidity impacts immune ageing in persistent Ag-specific T-cell responses. Research Training The student will receive expert training in immunological (e.g. high-dimensional flow cytometry & single cell sorting), molecular (STELA) and single cell sequencing techniques and will gain experience in systems-based approaches for data analysis. The project has been designed with flexibility to enable the student to steer the project and align it with their interests. Added value The student will work across disciplinary boundaries combining biological and mathematical approaches, and will benefit from numerous established local, national and international collaborations (e.g. Germany, Australia).
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