Project Details	
Project Code	IIAR27Ca Ladell
Title	Understanding cellular ageing of protective immunity to inform vaccine design and T-cell therapies
Research Theme	Infection, Immunity & Antimicrobial Resistance
Project Type	Wet lab
Summary	The risk of dying from infection is particularly high in the elderly and is related to ageing of the immune system. Immune cells called T-cells can confer long-term protection against infection and hence are critical for vaccine development. However, T-cell responses to infection become less effective with age, but the reasons for this are not yet well understood. You will examine T-cell dynamics using engineered protein technology, sophisticated imaging platforms (e.g., a FACSDiscover S8 with CellViewTM), molecular techniques (transcriptomics and telomere length assays), and bioinformatics to gain a better understanding of immune ageing to inform future vaccine design and immunotherapies.
Description	Immune cells called T-cells are very important for long-term protective immunity. Healthy humans are born with mostly naïve T-cells, i.e. T-cells that have not yet responded using their T-cell receptor (TCR) to a perceived foreign stimulus such as a pathogen. It is estimated that we are born with 10^8-10^10 different and specific T-cells where specificity is determined by their TCR. This T-cell diversity is also related to the Human Leukocyte Antigens (HLAs) that are inherited. The reason for the link between TCRs and HLAs is that HLAs present peptides derived from e.g. pathogens to T-cells. In fact, it is peptides from a pathogen rather than the whole pathogen that is recognized by T-cells. Each person has gene copies from the mother and the father of HLA-A, HLA-B, HLA-C genes (PMID: 36605212) and the HLA nomenclature is vast (https://hla.alleles.org/ pages/antigens/hla_antigens/). There are well-known HLA-disease links with the most well know link between HLA-B27 and ankylosing spondylitis (https://www.nhs.uk/conditions/ankylosing-spondylitis/causes/). While we understand a lot about TCRs, HLAs and the peptides HLAs present, many questions remain regarding the evolution of T-cell diversity, long-lived protective immunity and immunological ageing. What we know and what is the key question? We know that T-cells with different TCRs can recognize the same peptide presented by the same HLA. Some of these T-cells will recognize this peptide-HLA (pHLA) complex with higher and some with lower binding strength. T-cells that recognize the pHLA with higher binding strength will be triggered more than T-cells with a TCR that has lower binding strength. The assumption is that T-cells responding with their TCR to a pHLA with higher binding strength will multiply more than T-cells with a TCR with lower binding strength. When cells multiply their telomeres shorten unless they have an enzyme called telomerase that can stabilize telomere length. Telomeres are repeat DNA sequences that cap and protect the ends of chromosomes. When telomeres shorten, they can reach the so-called Hayflick limit, which is the point at which the telomeres cannot shorten any further

	and cells cannot divide further and ultimately die. Telomeres shorten in ageing cells when we age. The hypothesis is that due to ageing T-cells with TCRs that have higher binding strength for the pHLA are lost over time. This leaves behind T-cells with TCRs with lower binding strength to fight off infections with less force and this effect of immune ageing makes the elderly more susceptible to death due to infections. Therefore, the key question is whether the TCR binding strength of specific T-cells relates to their ageing. While scientists have tried to confirm that this is what is happening, they have not had the vast bank of pHLAs we have available and they also do not have the telomere length expertise. To answer this fundamental and related research questions, the student will learn how to: 1. Make pHLAs that they will label with fluorescent dyes and that they will use to identify T-cells using a technology called flow cytometry. 2. Design spectral flow cytometry experiments that will allow them to characterize in detail and sort-purify T-cells that recognize different viruses. 3. Determine the TCRs of single-sorted T-cells and they will sort T-cells not only based on pHLA recognition but also based on their TCR for downstream telomere length assessment. 4. Do the single telomere length assay. 5. Grow T-cell clones specific for the same or different viruses and they will assess how they age in the presence or absence of different agents in the culture dish over time. Their work will confirm or disprove a paradigm of immune cell ageing. There are numerous other unresolved questions regarding pHLAs and TCRs, e.g. considering that people are born with different combinations of HLAs, e.g. someone could have HLA-A2, HLA-B7 and HLA-C7, someone else could have HLA-A3, HLA-B27 and HLA-C4, and another person could have HLA-A3, HLA-B7 and HLA-C4, we do not know how the immune system decides which HLA to use to generate the biggest T-cell response to a given peptide froma pathogen and the consequences this may have for protective immunity. The student will become an expert in the T-cell field with unique skills, and this will help them formulate their own questions.
Can be completed part time?	Yes
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