Project Details	
Project Code	MRC22IIARCa Sewell
Title	Development of HLA-agnostic broad-spectrum cancer immunotherapies
Research Theme	Infection, Immunity, Antimicrobial Resistance & Repair
Summary	T-cell therapies are the biggest development in cancer treatment in over 50 years with some forms now given on the NHS. We work closely with industry to develop new immunotherapies for cancer. We have a bank of T-cell receptors (TCRs) that see most cancers from all people via several new ligands (e.g. Nat Immunol 21, 178). This project will characterise some of these "HLA agnostic" TCRs with a view to developing next generation TCR-T therapies for cancer.
Description	BACKGROUND Adoptive transfer of patient T-cells engineered to express a chimeric antigen receptor (CAR) specific for molecules on cancer cells has achieved remarkable success as a salvage treatment for B-cell leukaemia and is now provided on the NHS. Unfortunately, the triumph of CAR-T therapy has not been replicated with solid tumours (>99% of cancer). In contrast, tumour-infiltrating lymphocyte (TIL) and checkpoint inhibitor therapies demonstrate that natural T-cells can eradicate end-stage solid tumours in some patients. This success has heightened interest in engineering patient T-cells with successful T-cell receptors (TCRs) for "TCR-T" therapy. While there is mounting evidence that natural TCRs can effectively 'cure' some solid cancers, the HLA-restriction of conventional TCRs represents a major challenge to TCR-T approaches as the substantial variability in HLA-I genes across the population means that even the best HLA-restricted approaches are only applicable in a minority of patients. The ultimate TCR-T therapy would bypass HLA-restriction to enable targeting of shared cancer antigens in all individuals. Our recent discoveries now make this possible for the first time. We aim to understand the molecular mechanisms by which 'HLA-agnostic' T-cells recognise cancer and utilise these remarkable cells and their TCRs to identify the cell surface changes that distinguish normal from cancerous cells. WORK LEADING UP TO THE PROJECT We have a bank of >250 T-cell clones that recognise most cancer cell lines without the requirement for a specific HLA. These HLA-agnostic, unconventional T-cells exhibit a range of recognition patterns. All T-cells respond to primary cancer cells and remain inert to healthy cells. The Wellcome Trust recently funded us (£2M) to work on 17 of these TCRs. The successful student will be able to tap into our bank of T-cell clones and the infrastructure enabled by recent investment (>£7.5M). Most of our anticancer, HLA-agnostic T-cells were derived from patients that cleared end-stage solid cancers and persisted in patient blood following complete durable remission indicating that they are safe in vivo and may have the capacity to effectively eradicate solid cancer. AIMS AND PLAN OF INVESTIGATION AIM1: TCR prioritisation The first aim will involve prioritising ~3 TCRs for further work based on whether they recognise novel ligands and the number and type of cancers they recognise. It will be important to choose TCRs that function well when transduced into primary T-cells. AIM2: Confirmation that TCRs are HLA agnostic and recognise a broad range of cancer targets while remaining inert to heathy cells. AIM3: TCR ligand identification We have two established proven technologies for ligand identification – Whole genome CRISPR

	library screening as used to identify that MR1 presents cancer ligands (Nature Immunology, 21, 178-185) and antibody blocking as recently used by our collaborator Professor Julie Déchanet-Merville (DOI: 10.1126/sciimmunol.aba9010). These will be used in conjunction with our TCR replacement technology (https://doi.org/10.1182/blood-2017-05-787598) to identify the TCR ligands recognised by HLA-agnostic anticancer T-cells. AIM 4: Ligand comprehension and clinical exploitation It will be important to understand and harness the pathways that produce the distinguishing features that HLA-agnostic T-cells recognise at the surface of cancer cells. If the student gets this far then we anticipate that their work will become incorporated into the clinical pipelines of one of our industrial collaborators as happened with Mike Crowther's recent work as a Cardiff University PhD student. All of the above is feasible for a good PhD student as demonstrated by a student who recently undertook a PhD in this area in our laboratory (Nature Immunology, 21, 178-185).
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