Project Details	
Project Code	MRCIIAR26Ca Sewell
Title	From Survivor Blood to Curing Cancer
Research Theme	IIAR
Project Type	Wet lab
Summary	How do rare patients cure their own cancer? Some individuals with advanced cancers achieve complete remission, defying the odds without standard treatment. This project will investigate the natural T-cells responsible for these outcomes. Working with unique samples from exceptional survivors, you will explore how these T-cells recognise and eliminate cancer, sometimes across multiple tumour types and unrelated individuals. Using advanced T-cell engineering and CRISPR screening, you will uncover new cancer-specific targets with genuine therapeutic potential. This is a rare opportunity to help decode natural immunity to cancer and contribute to the development of the next generation of immunotherapies.
Description	**PREFACE** This studentship will run in parallel with Professor Andrew Sewell's current Wellcome Discovery Award, which focuses on identifying the antigens recognised by T-cells responsible for complete remission of late-stage metastatic cancer. Professor Sewell has held continuous Wellcome Trust funding for over 30 years and currently leads a small, well-resourced group in Cardiff University's Systems Immunity Research Institute that incorporates, an in-house CRISPR facility, NovoCyte FACS analyser, SONY MA900 FACS sorter and protein crystallography and biophysics suite. The successful student will benefit from an exceptionally productive and supportive research environment, with access to world-class facilities, mentorship, and cutting-edge immunology. The Sewell lab currently has a single PhD student, who will complete before this studentship begins, enabling focused supervision and dedicated access to lab resources. Previous PhD students in the group have gone on to become university professors, biotech founders, and senior partners in venture capital firms. **INTRODUCTION** While most patients with advanced solid cancers ultimately succumb to their disease, rare individuals achieve complete, durable remission - even in cancers such as stage IV pancreatic adenocarcinoma. We have collected and characterised samples from such exceptional survivors. In many cases, these include autologous tumour lines that the patients successfully cleared. These unique resources provide an unprecedented opportunity to uncover the mechanisms by which natural T-cells eliminate cancer. Preliminary work shows that the dominant, persistent T-cell clonotypes in some of these individuals often recognise a wide range of cancer types without requiring a specific HLA allele, a phenomenon we refer to as HLA-agnostic recognition. These data suggest that the T-cell receptors (TCRs) involved recognise widely shared, surface-accessible, cancer-enriched targets. Understanding these mechanisms could unlock next-generation immunotherapies with unprecedented tumour selectivity and population coverage.

RESEARCH QUESTION

What are the ligands recognised by HLA-agnostic, broadly tumoricidal T-cells derived from exceptional cancer survivors?

AIMS

1. To characterise the functional breadth and specificity of HLA-agnostic anticancer TCRs.
2. To identify and validate the ligands recognised by these TCRs.
3. To understand how these ligands arise on cancer cells and assess their potential as immunotherapy targets.

PROJECT BREAKDOWN

Year 1: TCR Selection and Functional Profiling

- Select candidate TCRs from our existing bank of over 60 broadly tumoricidal HLA-agnostic T-cell clones.
- Determine the cancer types recognised by each TCR using established functional assays (e.g., flow cytometry, cytokine release, killing assays).
- Training will be provided in advanced T-cell culture, immune phenotyping, and cell line handling.
- Functional profiling will be performed using both Jurkat reporter lines and primary TCR-engineered T-cells (TCR-T).

Year 2: Ligand Identification and Validation

- Perform genome-wide CRISPR-Cas9 knockout screens in target cancer cell lines to identify candidate ligands (see Nat Immunol 21:178–185 for precedent).
- Use antibody-blocking screens with broad antibody libraries as a complementary approach.
- Validate ligand identity through gain-of-function studies and re-expression in non-target cells.
- Integrate transcriptomic and proteomic datasets from our lab and collaborators to support findings.

Year 3+: Mechanistic Insight and Therapeutic Exploration

- Explore the pathways that give rise to ligand expression and determine why these markers are cancer-selective.
- Investigate potential for antibody, nanobody, CAR-T, or bispecific targeting of validated ligands.
- The student will be encouraged to lead publication efforts and present findings at national and international conferences.

STUDENT AUTONOMY

The student will have flexibility in shaping the project and may:

- Select from multiple candidate TCRs with distinct recognition patterns.
- Refine or develop novel experimental approaches.
- Formulate and test mechanistic hypotheses based on ligand identity and function.
- Pursue spin-off projects or translational opportunities that emerge from initial findings.

CONTINGENCY PLANS

Multiple validated, broadly tumoricidal TCRs are available. The student will be encouraged to pursue at least two in parallel, reducing risk. Ligand discovery for even a single TCR is expected to yield a high-impact publication.

	TRAINING AND DEVELOPMENT The student will receive training in: • Cellular immunology and T-cell engineering • Functional genomics and CRISPR screening • High-dimensional flow cytometry and bioinformatics • Collaborative science, experimental design, and scientific writing This project sits at the intersection of immunology, cancer biology, and translational medicine. It offers the opportunity to make foundational discoveries in cancer immunotherapy with direct potential to shape future treatments. **TRACK RECORD** Professor Sewell has successfully supervised 35 PhD students in the UK, all of whom completed within four years. Several have published first-author papers in Nature Medicine, Nature Immunology, Cell, and Journal of Clinical Investigation. Many former students now hold senior academic positions, including full professorships at leading UK institutions. Others have progressed into leadership roles in biotechnology and pharma, including CEO and Director-level positions in venture-backed companies. This track record demonstrates a consistent ability to support students in producing world-class research and launching successful careers. Sewell group PhD students are actively recruited by industry and are often offered high-paying roles before completing their PhDs.
Supervisory Team	
Lead Supervisor	
Name	Professor Andrew Sewell
Affiliation	Cardiff
College/Faculty	College of Biomedical and Life Sciences
Department/School	MEDIC
Email Address	sewellak@cardiff.ac.uk
Co-Supervisor 1	
Name	Dr Garry Dolton
Affiliation	Cardiff
College/Faculty	College of Biomedical and Life Sciences
Department/School	MEDIC
Co-Supervisor 2	
Name	Dr Hannah Thomas
Affiliation	Cardiff
College/Faculty	College of Biomedical and Life Sciences
Department/School	MEDIC
Co-Supervisor 3	
Name	
Affiliation	
College/Faculty	
Department/School	