



Project Title **Inducing leukaemic differentiation to prevent post-transplant relapse**
Group Leader Mark Williams
Research Group Leukaemia Immunology & Transplantation

This 4-year PhD studentship will be based at the Cancer Research UK Manchester Institute

Allogeneic haematopoietic stem cell transplantation is the only curative therapy for many patients with acute myeloid leukaemia (AML) and other poor-risk haematological malignancies. Recipients are 'conditioned' with chemo/radiotherapy before receiving blood-forming stem cells harvested from a donor. These stem cells repopulate the bone marrow and provide a new immune system which eliminates the cancer. However, disease relapse remains the most common cause of death and is due to failure of donor T cells to eradicate residual leukaemia. Reduced leukaemic MHC class II (MHCII) expression is common at post-transplant relapse and AML lacking MHCII elicits weaker donor T-cell responses. Professional antigen-presenting cells (APCs), such as macrophages and dendritic cells, activate CD4⁺ T cells by displaying antigenic peptides on MHCII together with co-stimulatory molecules. Our analysis indicates that leukaemic MHCII expression reflects a "forme fruste" of APC differentiation which could be modulated for therapeutic benefit. Differentiation can be induced in AML cells using many of the small molecule inhibitors currently being assessed in clinical trials. We hypothesise that drug-induced differentiation will drive leukaemic expression of MHCII, enhance CD4⁺ T-cell activation, augment CD8⁺ T-cell responses and promote immunological clearance of residual leukaemia cells.

Using human leukaemia cell lines, primary AML samples and murine models, we have shown that particular small molecule inhibitors induce leukaemic differentiation, producing large adherent cells that express MHCII, co-stimulatory molecules (eg. CD86) and produce the cytokines (eg. IL-1 β) needed to ensure robust T-cell activation and differentiation. We term these cells leukaemia-derived APCs (LD-APCs) and find that they elicit superior CD4⁺ T-cell activation, proliferation and differentiation, compared to undifferentiated leukaemia. In this project, the student will expand these findings to support their translation into clinical trials. This will involve testing a wide range of primary AML samples against a panel of inhibitors and their combinations to determine the optimal approach for inducing APC-like differentiation in primary AML with different genetic backgrounds, then confirming whether these cell states are equally capable of T-cell activation. We are also collecting samples from rare trial patients who have received experimental differentiation therapy and then received donor lymphocyte infusions, allowing the student to develop clear proof of concept.

We are looking for a hard-working, focused, ambitious person to join our friendly, interactive and excellent team. Our laboratory makes use of an extremely broad range of *in vitro* and *in vivo* techniques to study interactions between leukaemia and donor immune cells, with the aim of developing novel therapies for patients. Our activities span cutting-edge single cell sequencing and epigenetic approaches, through to murine models, biomarker development and clinical trials. We would be particularly happy to receive applications from individuals with a strong academic track record and Masters-level and/or other laboratory research experience in leukaemia, cancer biology or immunology.

This project would enable the successful candidate to work in the world-leading research environment of the CRUK Manchester Institute, whilst applying cutting-edge techniques to address a critical clinical problem. Students would gain broad exposure to immunology, haematology, oncology and



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transplantation. Upon completion, candidates would be well positioned to pursue a career in the fascinating and expanding field of cellular immunotherapy for cancer.