Project Title: "From Stem Cells to Cancer Immunotherapy: Engineering Human Blood and Immune-Cell Development"

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Research Group: Stem Cell Biology

Cell-based immunotherapies are transforming the treatment of cancer. CAR-T cells have produced remarkable clinical responses in patients with leukaemia, lymphoma and multiple myeloma and are now increasingly entering the clinic for the treatment of solid tumours, with encouraging advances across several cancer types. However, current CAR-T therapies are generally manufactured individually from each patient, making them costly, slow and difficult to produce at scale. A major goal for the field is therefore to develop "off-the-shelf" immune-cell therapies that could be manufactured in advance and made readily available to large numbers of patients. Human pluripotent stem cells offer an exciting solution: because they can be expanded almost indefinitely and genetically engineered, they could provide a renewable source of therapeutic immune cells, including conventional αβ T cells, unconventional γδ T cells, natural killer cells and other blood-cell types.

In this 4-year PhD project, you will investigate how human stem cells make blood and immune cells and use this knowledge to develop new platforms for their scalable production. A particular focus will be the haemogenic endothelium, a specialised population of endothelial cells that generates blood progenitors during embryonic development through the endothelial-to-haematopoietic transition (EHT). You will investigate the developmental signals, culture conditions and molecular pathways that control EHT and determine whether emerging blood progenitors acquire T-cell and other immune-cell potential. By manipulating these pathways, the project aims to improve the efficiency and reproducibility of human blood-cell production and direct differentiation towards immune-cell populations with potential applications in cancer therapy.

This multidisciplinary project sits at the interface of developmental biology, stem-cell engineering and cancer immunotherapy and will provide training in a broad range of cutting-edge technologies. These will include human pluripotent stem-cell and haemogenic endothelial culture, T-cell and immune-cell differentiation, high-dimensional and spectral flow cytometry, functional haematopoietic and immune-cell assays, high-throughput compound and pathway screening, genome engineering, single-cell transcriptomics and multi-omics, and in vivo models. The successful student will join a highly collaborative research environment and contribute to an ambitious programme seeking to understand and engineer human blood-cell fate. Ultimately, the project aims to establish robust and scalable approaches for producing next-generation off-the-shelf immune-cell therapies for both haematological and solid cancers.

Blood transfusions, bone marrow stem cell transplantation and cellular immunotherapies are fundamental to the treatment of malignant and non-malignant blood disorders. In particular, cell-based cancer immunotherapy has transformed the treatment of haematological malignancies. Autologous chimeric antigen receptor-

engineered T-cell (CAR-T) therapies have achieved remarkable clinical responses in leukaemia, lymphoma and multiple myeloma.

However, a major barrier to their widespread use is their autologous nature: current CAR-T products are manufactured individually from each patient, making them costly, time-consuming and challenging to produce at scale. Allogeneic, “off-the-shelf” immune-cell therapies could overcome many of these limitations, but conventional donor-derived cells carry important risks, including graft-versus-host disease and immune rejection.

An exciting alternative is to generate therapeutic immune cells directly from human pluripotent stem cells. Such an approach could provide a renewable and scalable source of engineered immune cells, including conventional αβ T cells, unconventional γδ T cells, natural killer cells and potentially myeloid cells.

During embryonic development, many of these blood and immune cells arise through a remarkable process known as the endothelial-to-haematopoietic transition (EHT), during which specialised haemogenic endothelial cells generate blood progenitors. Understanding and controlling this developmental transition therefore provides a unique opportunity to engineer new platforms for immune-cell production.

In this project, we aim to develop human stem-cell-based platforms for the scalable generation of immune cells with therapeutic potential.
You will investigate how developmental and environmental signals control the production and lineage potential of blood progenitors and will identify optimal culture conditions and molecular interventions that promote the generation of specific immune-cell populations.

The project will combine developmental biology, stem-cell engineering and cancer immunotherapy, using state-of-the-art approaches including:

- human pluripotent stem-cell and haemogenic endothelial culture
- T-cell and immune-cell differentiation
- high-dimensional and spectral flow cytometry
- haematopoietic progenitor and functional immune-cell assays
- high-throughput compound and pathway screening
- genome engineering
- single-cell transcriptomic and multi-omic approaches
- in vivo models of haematopoiesis and tumour immunity

The ultimate goal is to understand how human blood and immune-cell fate can be controlled and engineered, and to use this knowledge to establish robust platforms for producing next-generation off-the-shelf cellular therapies for cancer.