Clinical PhD Project 2024

Development of novel cellular immunotherapies

Principal supervisor's name: Dr **Mike Chapman**
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Principal supervisor's CRUK CC theme: Cancer Immunology Programme

Department for student registration: MRC Toxicology Unit
Department or institute where research will take place: MRC Toxicology Unit

Co-supervisor's name (if applicable): Rahul Roychoudhuri
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Postgraduate scheme: **Clinical Research Training Fellow (3-year PhD)**

PhD project outline:

Cellular immunotherapies have proved revolutionary in haematological malignancy, effecting cures in otherwise unsalvageable cancers. However, not all patients benefit, especially outside the non-Hodgkin lymphoma setting. Two of the major reasons for failure of CAR T-cell therapy are inappropriate antigenic target and failure of persistence of the infused cells. The Chapman and Roychoudhuri laboratories have been addressing these problems. Mike Chapman's laboratory has applied cutting edge cell surface proteomic techniques [1] to map the cell surface of cancer cells. They have developed algorithms to leverage these data to identify novel immunotherapeutic targets. Rahul Roychoudhuri's laboratory has been exploiting basic transcriptional biology to regulate the developmental state of T-cells. Of particular note has been their ability to balance stem and effector cell functions that will have significant implications for the success of cellular immunotherapies. Combining the knowledge and experience of both laboratories, the successful candidate will develop new CAR T-cell therapies. They will explore a wide range of CAR constructs against novel targets in conjunction with different cocktails of transcriptional modifiers in vitro. They will prioritize the best combinations to progress to in vivo experiments. They will work with a translational scientist to facilitate the development of a regulatory package to progress the best CAR T-cell construct towards early phase clinical trials.

PhD experimental plan:

The main thrust of this PhD will be determining how best to combine the technologies being developed in the Roychoudhuri and Chapman laboratories. The Roychoudhuri laboratory has strong preliminary data showing that T-cell stemness can be maintained without sacrificing effector cell function. The focus of this project will be on whether these findings are still valid in a CAR T-cell against a novel target. Using donor T-cells, initial work will involve engineering different transformation vectors and experimenting with different transformation protocols to modulate the profile of the derived CAR T-cell population. Then, these different populations will be tested in vitro and in vivo. Stemness and effector cell functions will be tested with a variety of outputs, including immunophenotyping, cytokine release, and functional readouts. In particular, the performance of different CAR T-cells in in vitro cell kill assays against human myeloma cell lines and primary myeloma samples will be assessed. The most promising CAR T-cells will be taken forward into xenograft assays. An important component of the xenograft work will be making modifications to the transformation protocol to make it compatible with existing regulatory

frameworks, facilitating the translation from pre-clinical work to clinical studies. Importantly, the Cancer Immunology Programme has access to the requisite infrastructure to produce clinical grade CAR T-cells.

Main techniques:

Tissue culture, processing primary human immune cells, vector cloning, viral transduction, flow cytometry, cytokine assays, in vitro cell kill assays, and xenograft and other in vivo models are likely to feature highly. Other approaches, such as various high-throughput assays, next generation sequencing, and proteomics may be used where appropriate.

Key references:

1. Anderson GSF, et al. Unbiased cell surface proteomics identifies SEMA4A as an effective immunotherapy target for myeloma. Blood. 2022 Apr 21;139(16):2471-2482. doi: 10.1182/blood.2021015161. PMID: 35134130.