

Project title:

Improving CAR-T Cell Therapy Using Radiotherapy And Oncolytic Viruses

Project Summary:

CAR-T cells are part of standard clinical care for some leukaemias and lymphomas, but have yet to make a significant impact on the immunotherapy of non-haematological solid cancers. We have previously shown, in immunocompetent murine models of melanoma and brain tumours, that CAR-T cells can be successfully combined with oncolytic viruses (OV) via the generation of so-called 'dual-specific CAR-T', in which the endogenous TCR of the CAR-T recognises the OV, so that effector cells can be expanded by further OV rechallenge (Evgin et al, Sci Transl Med 2022. PMID: 35417192). We are further currently i) testing the effects of local radiotherapy (RT) on the dynamics of CAR-T cell infiltration into tumours, and ii) testing a novel CAR-T targeting endosialin (Ash et al, J Immunother Cancer 2024. PMID: 38413223) in breast cancer. This project proposal will build on and develop our current work for therapy using CAR-T in non-Hodgkins lymphoma (NHL) and soft tissue sarcoma (STS). We will test combination of CAR-T with OV and RT, using our established anti-endosialin CAR-T and available models of CD19-expressing immunocompetent solid murine lymphoma models. For endosialin as a target, we will focus on STS because, unlike in breast cancer, where endosialin is expressed on tumor-associated pericytes and perivascular cancer-associated fibroblasts, endosialin is directly expressed in a significant percentage of STS (Thway et al, Br J Cancer 2016. PMID 27434038). Hence we will test anti-CD19 CAR-T for NHL, and anti-endosialin CAR-T in murine solid tumour models of NHL and STS, alone and in combination with RT and/or OV, seeking to improve on current clinical strategies (for NHL), and develop a novel immunotherapy approach (for STS). Mechanistically, these studies will include a number of approaches, including characterisation of the evolution of the TCR repertoire, and tracking of T cell dynamics using the Tocky transgenic mouse model, already established in our laboratory (Bozhanova et al, J Immunother Cancer 2022. PMID: 35338089).

Supervisory Team:

Primary supervisor: Prof Alan Melcher

Secondary supervisor: Dr Emma Nicholson

Associate supervisors: Dr Ernesto Lopez, Dr Charlotte Palwyn, Prof Clare Isacke

Clinical Specialities:

Haematology, Medical oncology.