Generation of alternative HLA-I restricted T cell receptors (TCRs) for Adoptive T cell Therapy of cancer

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This project aims to isolate and characterise new alternatives to HLA-I-restricted T cell receptors (TCRs) with high affinity that recognise immunogenic cancer-specific epitopes for TCR gene therapy of cancer.

Adoptive T-cell therapy (ATT) with CAR-T cells targeting the B-cell antigen CD19 has led to remarkable regressions in leukaemia and lymphoma patients, with depletion of mature, normal B-cells as an acceptable side effect. Translating this approach to solid tumors has proven difficult, with a major hurdle being the identification of suitable tumor-associated autoantigens as T-cell targets that are effective in killing tumors without causing dose-limiting pathology in normal somatic tissues. Another limitation of the CAR strategy is that it only targets antigens expressed on the cell surface.

TCR gene therapy targeting HLA-restricted cancer epitopes offers a promising alternative in this regard. The polymorphic classical HLA-I molecules, however, are subject to some limitations in the breadth of applicability of the corresponding TCRs and tumor immune escape due to loss of HLA class I expression and/or deficiencies in antigen processing. In this project the researchers take advantage of generating highly avid TCRs from a humanised mouse model harboring the entire human TCRα/β loci that has additionally been modified to express alternative HLA-I molecules.