GENETICALLY ENGINEERING T CELLS TO REDUCE THE RISK OF AUTOIMMUNE CROSS-REACTIVITIES IN CANCER T CELL THERAPIES

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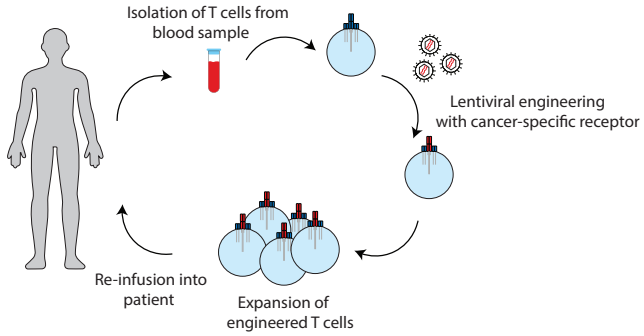
The problem



Adoptive T cell therapies involve the engineering of a patient's own T cells with a novel cancer-specific receptor, followed by the re-infusion of the engineered T cells into the patient to target their tumour. Even though these therapies have shown promising clinical responses they can also carry a safety risk. For example, in one clinical trial, two patients that received T cells engineered to recognise a cancer peptide (MAGE-A3) died due to an autoimmune reaction to an unrelated off-target peptide in the heart (Titin). Therefore, there is an urgent need to identify methods to reduce the cross-reactivity of T cells to increase the safety of these therapies.

Methods

We isolate T cells from blood donors and engineer them with a cancer-specific receptor. We then genetically edit the T cells to identify modifications that abolish activation against off-target peptides, whilst maintaining potent activation against the on-target cancer peptides.

Key results

We have identified a combination of genetic modifications that generate super selective T cells. For example, we have demonstrated that our engineered T cells can recognize the MAGE-A3 cancer peptide, but do not become activated against the Titin peptide from the heart which previously caused two deaths in a clinical trial. Therefore, our approach could enable the development of safer T cell therapies.