

Genetically Modified T Cell Therapies for Cancer - Basic Facts

T cells are cells of the immune system that fight infection and can attack virally infected or tumour cells. T cells, via their surface T cell receptor, scan the cells of the body for foreign antigens and diseased cells. When there is a match, the T cell is activated and unleashes an attack on the target cell, including the release of cytokines, which results in the elimination of the target cell. Tumours should be targets for T cells and indeed tumour specific T cells have been isolated from some tumour patients. However, tumours use several immune subversive approaches to render themselves less susceptible to immune attack, limiting the effectiveness of the circulating T cells. Such strategies include reduced expression of molecules and target antigens, the establishment of an inhibitory microenvironment and the ability of the cancer cells to dedifferentiate to evade detection in response to inflammatory cues provided by tumour-specific T cells. Thus in many cases the immune response ceases to be effective against tumour cells.

Scientists are looking to harness the power of T cells by genetically modifying them to redirect the target of the T cell receptor and hence increase their activity against tumour cells. There are two classes of genetically enhanced T cell therapies; gene modified T cell receptor (TCR) therapies and chimeric antigen receptor (CAR) therapies. The defining difference between the two classes of T cell therapy is the type of antigen target (Figure 1); CAR therapies directly recognise the antigen with which they interact (external antigens) whilst TCR therapies require cellular presenting elements such as HLA molecules (internal antigens). This difference is reflected in the respective active moieties. TCR therapy specificity is determined by the genetic transfer of specific T cell receptor whereas a CAR therapy is a fusion receptor coupling antibody-like recognition of the target with T cell activating signals. For both technologies persistence of a given therapy is linked to the properties of the T cell from which the cells were derived as well as the immune environment into which they are infused.

The majority of genetically modified T cell therapies are tumour immunotherapies. Recent clinical data has indicated that the T cell therapies can be very effective against the target tumour, removing the tumour cells at a faster rate than is seen with traditional immune therapies. As the tumour cells are lysed, cytokines are released which can result in tumour lysis syndrome, which in extreme cases can lead to an uncontrolled immune reaction; a cytokine storm. Tumour cell lysis is a key outcome for T cell therapy and a balance will need to be achieved between desired and undesired effects. As the target for the T cells are self-antigens, there is the possibility that these antigens may also be expressed on normal human tissue with the risk of on-target/off-tumour cytotoxic activity. Recently published data has shown what can happen when off tumour activity occurs; four patients have died following administration of genetically engineered TCR T cells^{1,2}. Scientists are employing a range of new technologies to better understand the expression pattern of candidate target antigens to mitigate this risk.

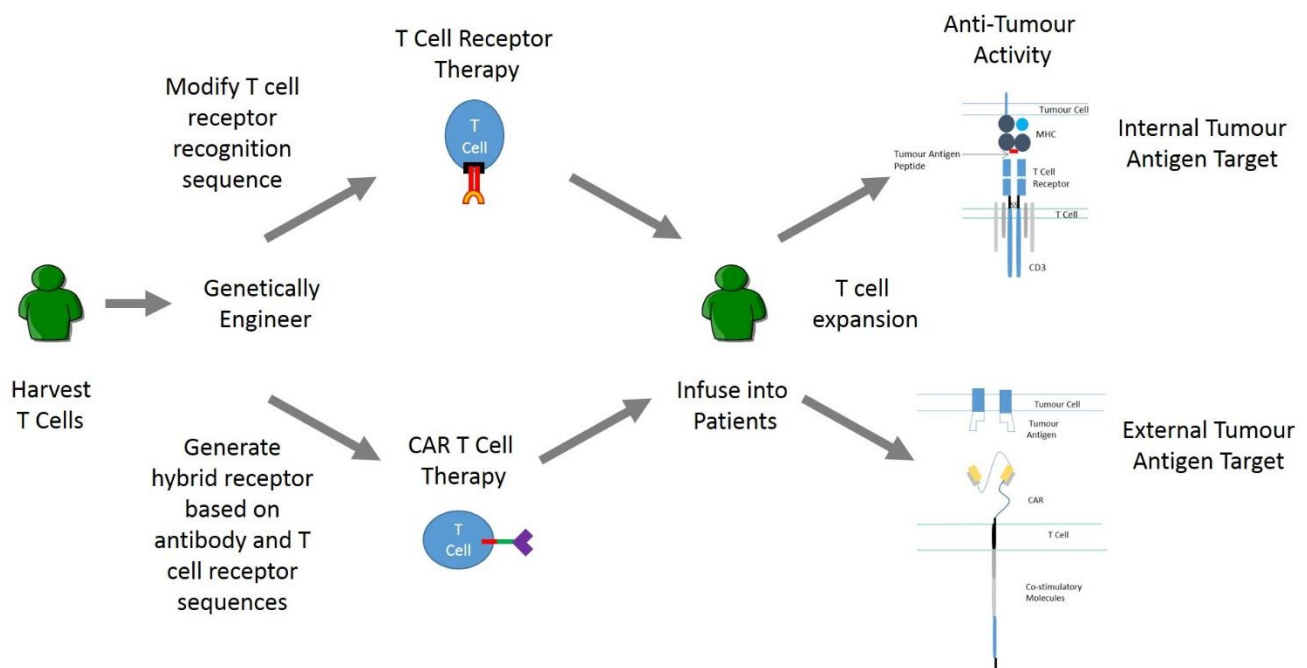


Figure 1 T cells are harvested from the patient and genetically engineered with either a new T cell receptor or a receptor based on a recognition sequence of an antibody, combined with T cell activating sequences. The genetically modified cells are re-infused into the patient and the T cells should be activated when they encounter the specific antigen target.

There has been significant progress in the development of gene modified T cell therapies and the first reports of benefits to patients are being reported in clinical trials with complete responses being reported in both trials of TCR and CAR T cell therapies. Recently, in a trial run by the Children's Hospital of Philadelphia and the University of Pennsylvania 89% of children and adults with a highly aggressive form of relapsed and refractory acute lymphoblastic leukemia showed no evidence of cancer after receiving a CD19 CAR T cell therapy^{3,4}. Although 6 patients subsequently relapsed from complete response, 64% of patients remained in complete response at a median of 2.6 months follow up (range 1.2-15 months) with one patient showing CR at the 15 month follow up, demonstrating the potential clinical benefit of this class of therapies. Patients who have shown complete responses typically exhibit greater persistence and survival of the gene modified T cells. Consistency of manufacturing process, patient conditioning regimens, cytokine support and the T cell subset transduced are all variables that may impact efficacy and are the subject of ongoing research. Clinical trials targeting optimal tumour target and clinical regimens are now warranted.

Research efforts are now focused on addressing the key challenges of T cell target specificity, persistence and ability to exert the desired anti-tumour effects as well as identifying new target antigens. These programmes are advancing the clinical translation of genetically modified T cell receptor therapies.

References

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