No More Shots in the Dark: Imaging and quantifying CAR T-cells

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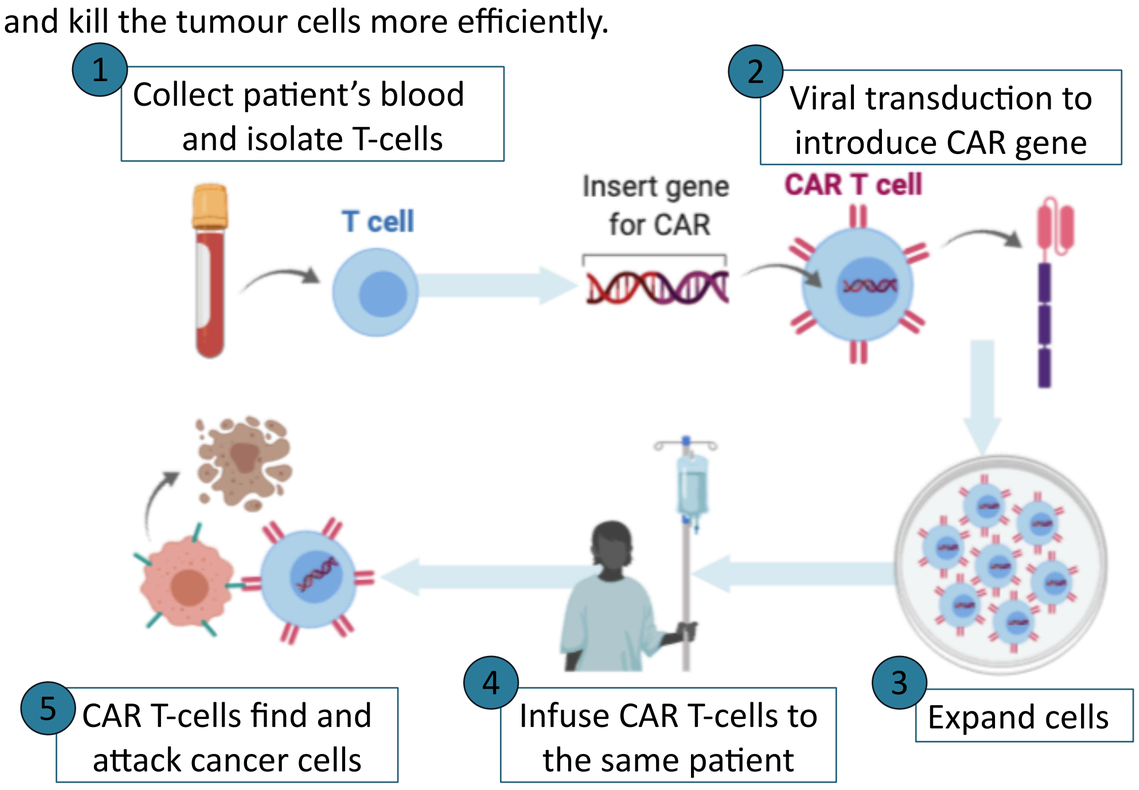
What is T-cell based immunotherapy?

Immunotherapy aims to boost our own immune system to fight tumours. Chimeric antigen receptor (CAR) T-cells are T-cells that have been genetically engineered in the laboratory to express an antigen receptor capable of recognising a specific surface antigen expressed in the patients´ tumour cells.

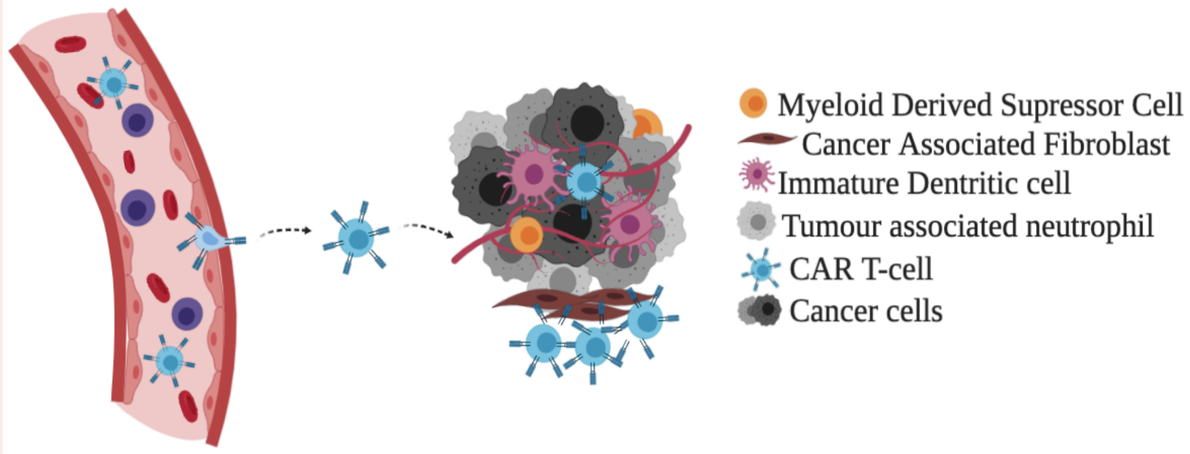
After *ex vivo* proliferation, these CAR T-cells are adoptively transferred back to the patient with the hope that they will selectively recognise the target antigen and kill the tumour cells more efficiently.



Which cancers can it be used on?

CAR T-cell immunotherapy has shown promising results in the treatment of haematological tumours; however, the success rate drastically decreases when targeting solid tumours.

In contrast to liquid tumours, solid tumours are formed by several cell types embedded in an unfavourable tumour microenvironment (TME). CAR T-cells need to migrate to the tumour site, penetrate and survive in a heterogenous and immunosuppressive TME depleted of oxygen and nutrients.

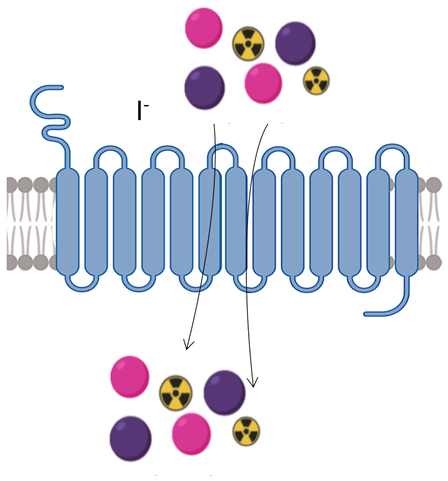


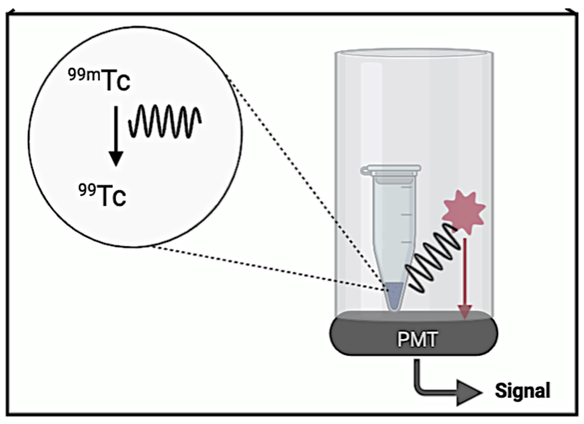
It is still unclear to what extend these challenges affect T-cell behaviour. Understanding the effect of the TME would facilitate the development of more successful clinically relevant CAR T-cell products for solid tumours.

A universal technique to track CAR T-cells

Repetitive non-invasive *in vivo* imaging of CAR T-cells could be the solution, helping us improve our understanding on T-cell therapeutics for solid tumours.

To track and image CAR T-cells, a reporter gene, human sodium iodide symporter (hNIS), is expressed on the cell membrane. Upon intravenous injection of the well-known radiotracer technetium pertechnetate ($^{99m}TcO_4^-$), the hNIS transports and concentrates it inside the CAR T-cell.

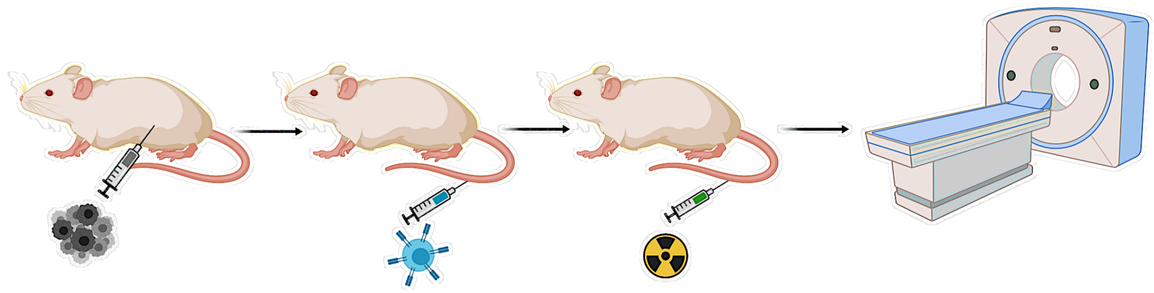




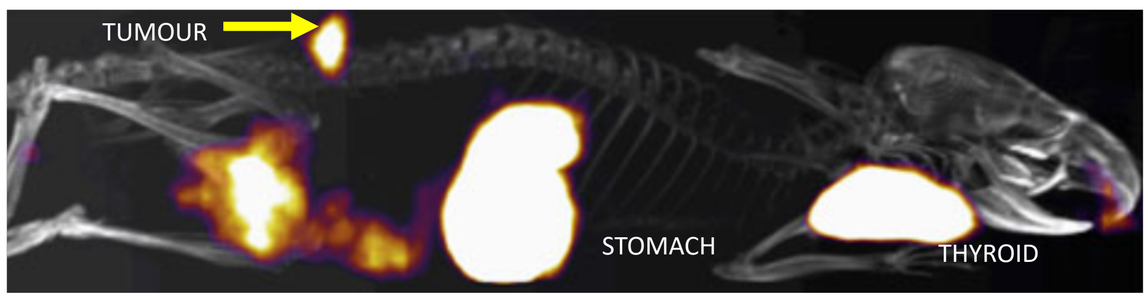
Since $^{99m}TcO_4^-$ is an unstable radioactive substance, it decays to a more stable status $^{99}TcO_4^-$ while releasing a gamma photon. This photon can be measured with a gamma counter and gives us information of the location of the CAR T-cells in the body.

Promising results

Our lab have co-expressed a PSMA-targeting CAR with hNIS to treat prostate cancer. These CAR T-cells were able to kill the tumour *in vitro* and $^{99m}TcO_4^-$ only accumulated in live cells. Prostate cancer cells were then injected in immunodeficient mice to stablish xenografts which were then treated with CAR T-cells. To image the CAR T-cells $^{99m}TcO_4^-$ was injected prior SPECT scan.



They showed the spatial accumulation of CAR T-cells in the tumour site and the temporal correlation between accumulation of CAR T-cells and reduction of tumour burden. Thus, demonstrating that CAR T-cells do travel to the tumour site and are functional.



Emami-Shahri et al., 2018

From animal models to imaging CAR-T cells in patients

Our lab have shown for the first time that human CAR T-cells can be repeatedly imaged *in vivo* using a hNIS-based reporter system. However, we need to gain a better understanding of the behaviour of CAR T-cells once they have reach the tumour.

We now aim to make this approach quantitative to determine the number of CAR T-cells reaching the tumour, their proliferation capacity and persistence over time. Addressing these questions will accelerate the translation of these imaging technique to the clinic.

My PhD project aims to explore the relationship between reporter gene, tracer and host and find answers to such questions as:

- How many cells are detected?
- What are the limitations when using hNIS?
- What are the tracer kinetics?
- What is the limit of detection when using SPECT/CT?
- How many CAR T-cells are needed to reduce tumour burden?