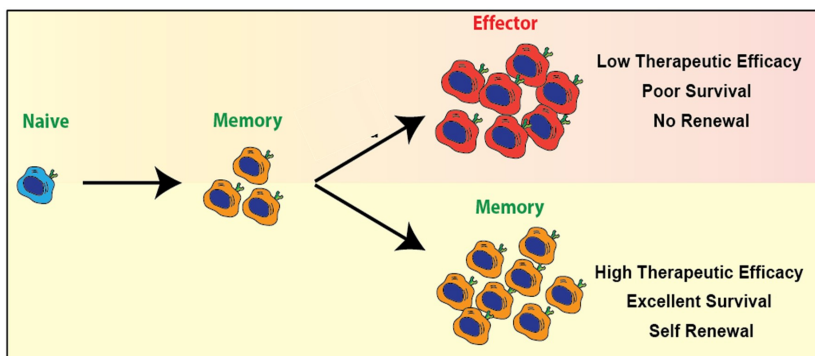




Enhancing the efficacy and persistence of adoptive T cell therapies

Adoptive therapies such as CAR-T and TCR are an emerging opportunity with potential to increase efficacy and broaden patient populations in oncology. There is increasing clinical data to support the hypothesis that the efficacy of these therapies is associated with persistence and expansion of T cells.

Ex vivo conditioning of human T cells and CAR-T cells with octyl S-2-hydroxyglutarate to maintain a memory-like state, improve persistence and efficacy of T cell immunotherapies.



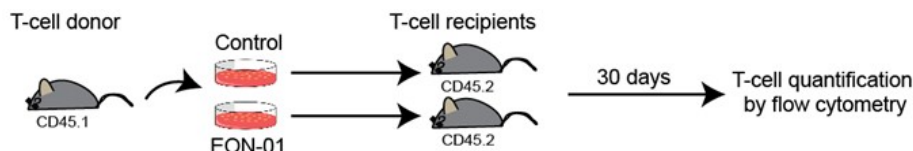
The problem

Highly differentiated T cells result in low persistence that reduces efficacy and promotes cytokine release

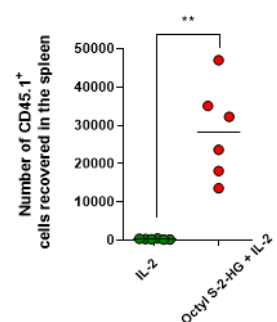
The goal

Memory T cells result in increase persistence and self renewal that increase efficacy

Apollo Therapeutics, working closely with Prof. Randall Johnson and his team in the Department of Physiology, Development & Neuroscience at the University of Cambridge have developed a small molecule that promotes memory T cell populations - *octyl S-2-hydroxyglutarate* - and have demonstrated applicability to human CAR-T systems.



Ex vivo treatment with octyl S-2-HG enhances persistence 80-fold in vivo



Licensing opportunity: octyl S-2-hydroxyglutarate

- Promotes memory T cell populations, conferring persistence and proliferation that translates into enhanced anti-tumour efficacy
- Characterised in mouse and human systems
- Fully compatible with human CAR-T lentiviral transduction protocols
- Opportunity for clinical differentiation

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Background

One of the current clinical challenges associated with CAR-T therapies is the lack of T cell persistence upon transfer back into the patient. The *ex vivo* generated T cells become exhausted during expansion in culture, have low persistence, and thus only provide short term immune-surveillance which impacts clinical efficacy. Less differentiated memory T cells display improved expansion and persistence, which translates into enhanced anti-tumour activity.

Key Features

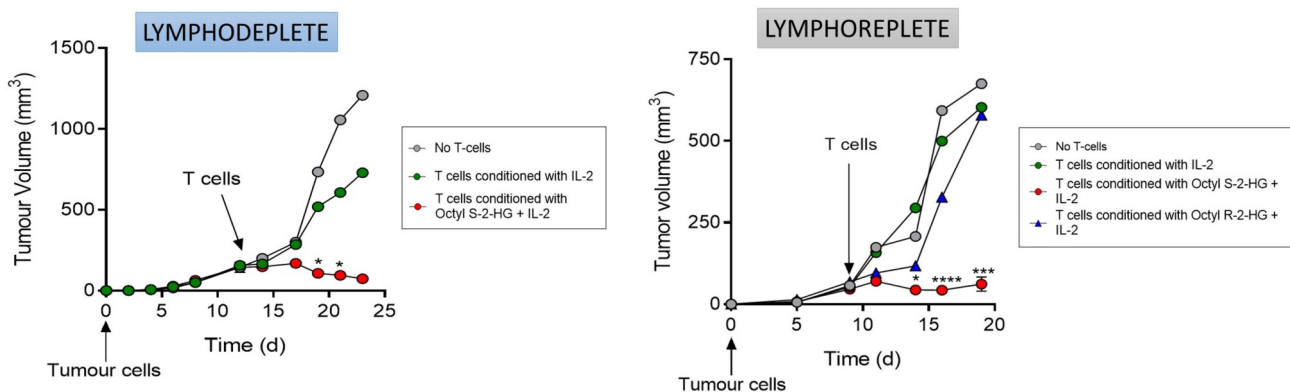
Pre-conditioning T cells with octyl S-2-HG in combination with IL-2 increases memory T cell populations (evidenced by memory-specific markers) resulting in enhanced expansion, persistence, recall and efficacy

In vivo data: adoptive transfer of T cells treated *ex vivo* with octyl S-2-HG combined with IL-2

- Enhances persistence >80 fold at day 30
- Increases anti-tumour efficacy in the EG7-OVA tumour model

Beneficial properties: octyl S-2-HG confers additional pharmacology

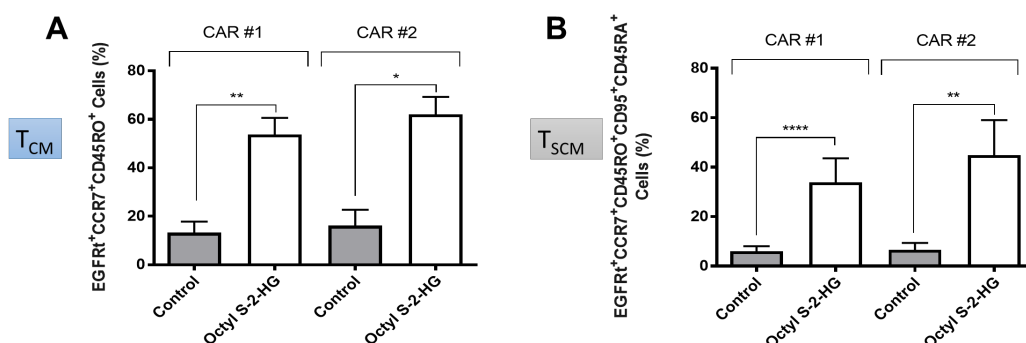
- Promotes *in vivo* persistence of T cells in lymphoreplete and irradiated hosts
- Increases homeostatic proliferation of adoptively transferred cells in irradiated mice
- Promotion of a recall response of adoptively transferred T-cells *in vivo*
- Increases efficacy in lymphodeplete and lymphoreplete mice



Ex vivo treatment with octyl S-2-HG enhances tumour efficacy in vivo

Efficacy of OT-I CD8⁺ T cells treated *ex vivo* with octyl S-2-HG following adoptive transfer into lymphodeplete and lymphoreplete EG7-OVA tumour bearing animals. (*p≤0.05; ***p≤0.001; ****p≤0.0001).

Human system: Treatment with octyl S-2-HG is compatible with transduced human CAR-T cells and promotes a memory cell phenotype. Lentiviral transduction efficiency is unaffected by octyl S-2-HG addition (data not shown).



Ex vivo treatment of CAR-T cells with octyl S-2-HG enhanced memory phenotype

Memory phenotype (A) T_{CM} central memory and (B) T_{SCM} stem cell memory of CAR-transduced activated naïve human CD8⁺ T cells following treatment with octyl S-2-HG. IL-2 was present throughout the conditioning. Two different anti-CD19 CAR constructs were used (* p≤0.05; ** p≤0.01; **** p≤0.0001).

Publications

Tyrakis et al., Nature 2016 reported that mouse T cells can be maintained in a memory-like state after treatment with 2HG. The technology is protected by published patent WO2017076602.