A novel strategy to eradicate HIV using CD8 CAR T cells

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Background: The latent HIV reservoir in CD4 T cells remains a major barrier to a HIV cure. Latency-reversing agents are suboptimal in reactivation, and reactivated HIV can evade CD8 T-cell-mediated clearance because of immune exhaustion and/or viral escape mutants. This study aimed to restore CD8 T-cell antiviral activity using chimeric antigen receptors (CARs) derived from the single-chain variable fragment (scFv) of broadly neutralising antibodies (bNAbs) targeting highly conserved gp120 epitopes. We hypothesised that these CD8 CAR T cells would enhance the recognition and elimination of HIV-infected cells.

Methodology: CD8 CAR T cells were engineered to express scFv from potent bNAbs PGT121 (targets V3 loop of gp120), VRC07 or MEL1872 (both target CD4 binding site) in single CAR constructs. Additionally, two bNAbs were co-expressed in a tandem CAR (TanCAR) configuration to limit viral escape from single-epitope targeting. Their cytotoxic function against HIV-infected cell lines and autologous primary CD4 T cells was assessed using flow cytometry.

Results: PGT121 and VRC07 CAR T cells significantly killed infected SupT1 cells ($p<0.05$). However, only PGT121 CAR T cells achieved significant killing of in vitro primary CD4 T cells ($p<0.05$). Therefore, VRC07 was replaced with MEL1872, which showed much higher binding affinity to gp120. Consequently, TanCAR T cells co-expressing PGT121 & MEL1872 were generated. Single and TanCAR efficiency at eliminating infected autologous T cells will be assessed.

Conclusion: CAR T cells have the potential to reduce the latent reservoir upon reactivation. The most potent CAR T cells that significantly kill in vitro infected CD4 T cells will progress to ex vivo and in vivo testing. Therefore, we will test HIV reactivation in CD4 T cells derived from people living with HIV and subsequently target them with appropriate CAR T cells. In parallel, we will assess CAR T-cell efficacy in vivo using a humanized mouse model.

Disclosure of interest statement: None