A novel strategy to eradicate HIV using CD8 CAR T cells

Rana H[1], Duette G[1], Gowrishankar K[2], Micklethwaite K[2], Purcell D[3], Cunningham A[1], Nasr N[1]

1Centre for Virus Research, The Westmead Institute for Medical Research, Westmead NSW 2145
[2]Centre for Cancer Research, The Westmead Institute for Medical Research, Westmead NSW 2145
3Department of Microbiology and Immunology, The Peter Doherty Institute for Infection and Immunity, Melbourne, 3000

Background: The latent HIV reservoir in CD4 T cells remains a barrier for a HIV cure. Latency reversing agents are suboptimal in reactivation, and awaken HIV evades detection by CD8 T cells as it mutates and downregulates MHC Class I expression to prevent its recognition by CD8 T cells. Furthermore, CD8 T cells are exhausted and dysfunctional in chronic HIV. Broadly neutralising antibodies (bnabs) control HIV replication by binding to highly conserved regions of gp120. Therefore, we engineered CD8 T cells with chimeric antigen receptors (CARs) to restore their antiviral function.

Methodology: We generated CD8 CAR T cells expressing the single chain variable fragment (scfv) of the most potent bnabs PGT121 (targets V3 loop of gp120), VRC07 and MEL1872 (target CD4 binding site) or a tandem CAR expressing two bnabs (TanCAR) to avoid resistance to a single CAR. Their cytotoxic function against HIV infected cells was assessed.

Results: PGT121 and VRC07 CAR T cells killed efficiently infected SupT1s but in primary CD4 T cells significant killing was achieved only by PGT121 CAR T cells. This was due to high affinity binding of PGT121 but not VRC07 to gp120 on infected primary T cells. Therefore, VRC07 was substituted with MEL1872 that showed much higher affinity binding than VRC07 and a significant killing. TanCAR T cells expressing PGT121 & MEL1872 were generated and they also killed infected autologous T cells.

Conclusion: We have previously shown that IFNa8 can reactivate latent HIV in in vitro infected CD4 T cells. With IFNa reactivation and dual targeting of gp120 by CD8 CAR T cells, we hypothesise a new strategy to eradication/reduce the latent reservoir. We are currently testing HIV reactivation by IFNa8 in latently infected humanised mice and CD4 T cells derived from people living with HIV to then target them with CAR T cells.