Investigating ADCC and CAR NK/T cell activities against HIV-1 cell-to-cell transmission

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BACKGROUND

Despite the success of antiretroviral therapy in controlling HIV-1 replication, achieving a cure remains a significant challenge. One obstacle to blocking HIV-1 replication is the efficient cell-to-cell transmission (C-CT) of HIV-1, which is highly resistant to broadly neutralizing antibodies (bnAbs).
Here we studied the effects of immune-based strategies, including antibody-dependent cellular cytotoxicity (ADCC) and chimeric antigen receptor (CAR) NK/T cells, on HIV-1 transmission between cells.

METHODS

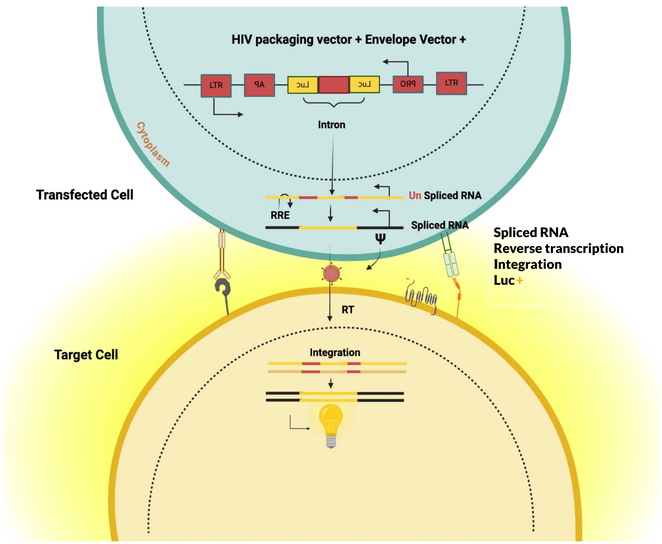
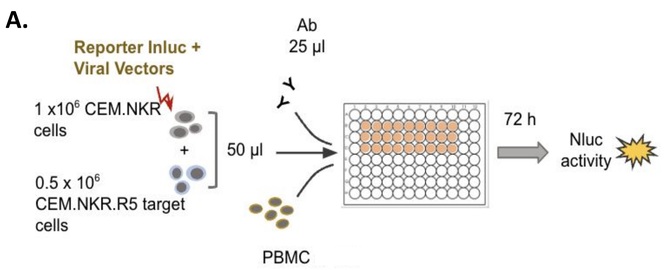
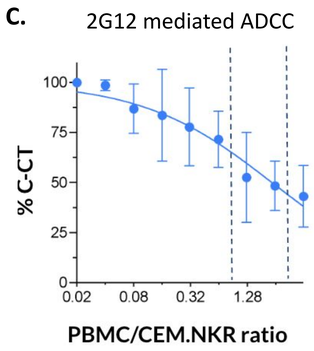
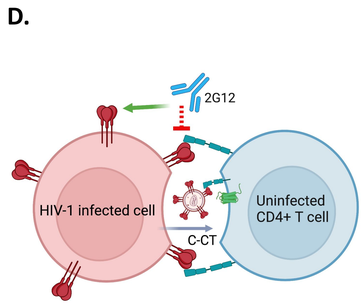


Fig 1: An improved reporter vector for ultrasensitive detection of HIV-1 cell-to-cell transmission between cells. The vector contains engineered elements in reverse orientation: a promoter (PRO), 5′- and 3′-portions of luciferase (luc) gene with an intron, and a polyA (PA) signal. The splice-donor (SD) and splice-acceptor (SA) sites are not reversed, preventing the splicing of the mRNA transcribed from PRO. Only RNA packaged into virions, reverse transcribed, and integrated into the host genome enables Luc expression from PRO.







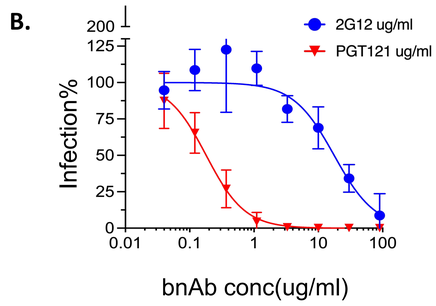
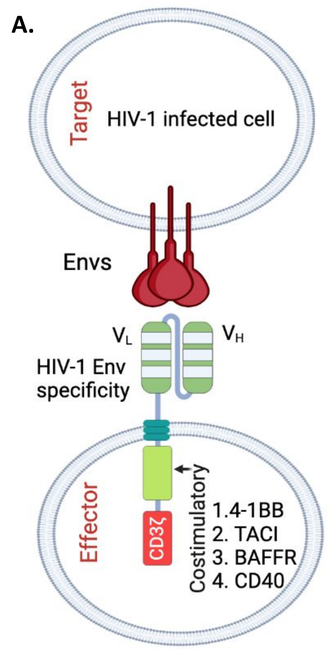
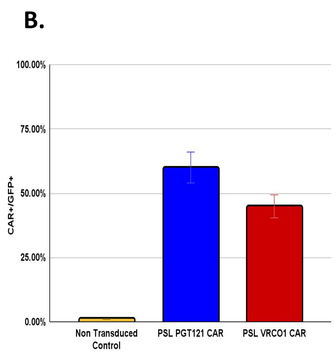


Fig 2: A. Experimental set up to test the effects of ADCC on HIV-1 C-CT. **B.** 2G12 is completely ineffective in inhibiting C-CT **C.** In the presence of PBMCs, 2G12 mediates the inhibition of C-CT. **D.** This suggests that HIV-1 Envs are also expressed outside of the synapse.

RESULTS





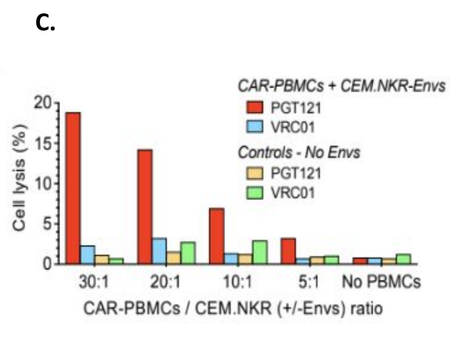


Fig 3: CAR-PBMCs activity against HIV-1 C-CT. **A.** A scheme of CAR components. **B.** Expression of PGT121 and VRC01 CARs in human PBMCs following lentiviral-mediated gene transfer. **C.** Lysis of CEM.NKR cells expressing HIV-1 Envs by PGT121- and VRC01-CAR PBMCs.

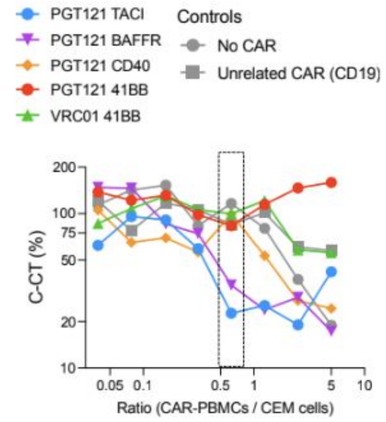


Fig 4: Effects of CAR-PBMCs with different costimulatory domains on C-CT of a replication competent HIV-1 between CEM.NKR T cells.

CONCLUSIONS & FUTURE DIRECTIONS

These results provide proof of the principle that targeting HIV-1 cell-to-cell transmission through ADCC and CAR NK/T cell therapies can overcome the limitations of bnAbs. This study offers the evidence to test these approaches to effectively target HIV-1 C-CT, highlighting their potential in studying HIV-1 treatment strategies.

ACKNOWLEDGMENT: This work was supported by the NIAID U01 grant 1U01AI169587

REFERENCE: Mazurov, D., & Herschhorn, A. (2024). Ultrasensitive quantification of HIV-1 cell-to-cell transmission in primary human CD4+ T cells measures viral sensitivity to broadly neutralizing antibodies. mBio, 15(1), e0242823. https://doi.org/10.1128/mbio.02428-23

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