HIV-resistant Dual CAR T cells targeting CD19 and HIV concurrently control HIV replication and B cell lymphoma in vivo

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Infusion of CD19-directed chimeric antigen receptor (CAR) T cells (CARTs) can result in robust CART expansion, long-term CART persistence, and durable remissions in B cell malignancies. We hypothesized that leveraging this expansion and persistence could enable sustained HIV control by engineering IL-18 secreting CD19 CARTs to co-express an HIV-specific CAR and a signaling-deficient C34-CXCR4 HIV fusion inhibitor (C34-CXCR4*), thereby generating HIV-resistant CD19/HIV dual CARTs. These CD19/HIV dual CARTs functioned as well as single CAR expressing CARTs toward a single target indicating no loss of activity occurred by co-expressing the CARs in the same cell. In a humanized mouse model of leukemia infused with CD4 T cells from a person with HIV (PWH), autologous CD19/HIV dual CARTs achieved tumor eradication comparable to that of CD19-only CARTs, demonstrating preserved antitumor efficacy. Notably, a CD19.BBζ–IL-18 CAR combined with a CD4.28ζ-C34-CXCR4* HIV-specific CAR exhibited enhanced T cell expansion and persistence and superior HIV and tumor control. Together, these findings identify CD19/HIV dual CARTs as a promising strategy to maintain a robust population of HIV-specific CARTs to control viral rebound, while simultaneously treating B cell malignancies, advancing CART based approaches toward durable HIV remission.