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Novel CD4-based bispecific chimeric antigen receptors provide potent and targeted killing of HIV-infected cells: a potential functional cure strategy

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Background: Durable virus control after cessation of antiretroviral therapy is a much sought after goal towards a 'functional cure' of HIV infection. We are developing strategies based on targeted killing of HIV-infected cells by T cells genetically modified to express CD4-based bi-specific chimeric antigen receptors (CARs) targeting the HIV-1 Env glycoprotein on the surface of HIV-infected cells. We recently reported highly potent and broad suppression of HIV-1 infection with transduced T cells expressing a novel CAR containing a portion of CD4 (D1D2) linked to an scFv of the 17b human monoclonal antibody against the highly conserved CD4-induced coreceptor-binding site of gp120. Encouraged by these results, we are designing bi-specific CARs with alternate second motifs with the goal of retaining high potency and breadth but minimizing potential immunogenicity.

Methods: In our new CAR design, the CD4 portion is linked to the carbohydrate recognition domain (CRD) of a human C-type lectin that specifically recognizes the high-mannose glycans on gp120. Alternative CRDs were derived from DC-SIGN, L-SIGN, MBL-2 and Langerin. T cells expressing experimental and control CARs (generated by retroviral transduction of PBMC from healthy donors followed by ex vivo expansion) were mixed at various ratios with autologous PBMCs infected with HIV-1; virus suppression was assessed at 8 days.

Results: The bispecific MBL-2 and Langerin CD4-CRD CARs exhibited superior HIV-1 suppressive activity compared to a monospecific CAR containing the CD4 region alone. Most importantly, the bispecific CARs were completely devoid of the undesired activity of rendering CCR5-positive CAR-transduced cells susceptible to HIV-1 infection, a property observed with the monospecific CD4 CAR. Considering the reduced immunogenic potential of a CRD compared to an scFv containing variable regions, we have begun testing our most potent CD4-CRD CARs for anti-HIV-1 activity in humanized BLT mice.

Conclusions: The novel bispecific CD4-CRD CARs offer superior potency compared to a monospecific CD4 CAR, without the potentially deleterious effect of rendering transduced CD8 T cells susceptible to HIV infection. The presumed minimal immunogenicity of the all-human non-variant CD4-CRD CARs makes them prime candidate for a functional cure strategy based on adoptive transfer of autologous T cells genetically modified for targeted killing of HIV-infected cells.