Towards a functional cure of HIV Infection using a novel CD4-based chimeric antigen receptor

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Major research efforts are currently underway to achieve 'functional cure' of HIV whereby virus suppression is maintained in the absence of antiretroviral therapy. Cell-based therapies are gaining momentum as a testable approach in this front. Following the clinical success of adoptive transfer of chimeric antigen-receptor (CAR)-modified T cells as a treatment for hematological cancers, we designed three CAR constructs with identical transmembrane domain and intracellular signaling domains linked to different extracellular antigen-binding moieties which target highly conserved receptor-binding sites on HIV Env. The extracellular targeting moieties are derivatives of the primary receptor CD4, either alone (CD4 CAR) or attached to the 17b scFv (targeting the coreceptor binding site) via a long linker (35 aa; CD4-35-17b) or a short linker (10 aa; CD4-10-17b). Our previous studies indicated that the corresponding soluble bifunctional protein with a long linker (CD4-35-17b) neutralized HIV with extreme potency and breadth, presumably due to simultaneous binding of both CD4 and 17b moieties to the same gp120 subunit; a protein with a linker too short for simultaneous binding (as in CD4-10-17b) showed weak potency.

We compared the 3 CAR constructs to test alternative concepts on the relationships between molecular binding affinity and target cell killing potency.

In our in vitro studies, peripheral blood CD8+ T cells transduced with each CAR secreted IFN-γ upon Env engagement and killed Env+ target cells. Importantly, for the suppression of HIV-1 infection of PBMCs, the CD4-10-17b CAR showed highest potency, followed by the CD4-CAR and the CD4-35-17b CAR being less effective. This result supports a model whereby cell killing is optimal when the effector/target affinity is sufficiently low to enable serial triggering, as presumably is the case for the CD4-10-17b CAR. We also noted that the CD4 CAR rendered CCR5+ cells susceptible to HIV infection, an undesired activity not observed with either of the CD4-17b CARs. Thus the novel CD4-10-17b CAR offers superior potency without the potentially deleterious effect of the CD4 CAR, for durable targeted cell killing to achieve a functional cure.

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