HIV-1-Specific Chimeric Antigen Receptors Based on Broadly Neutralizing Antibodies.

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Funding Grants: Stem Cell Programming With Chimeric Antigen Receptors to Eradicate HIV Infection

Public Summary:
Despite remarkable advances in treating HIV infection with drugs that allow people to survive long term, these drugs do not cure infection and must be taken life-long. A true “cure,” replacing the need for ongoing treatment that is expensive, potentially toxic, and monitoring-intensive, remains elusive. An arm of the immune system, “cytotoxic T lymphocytes” (CTLs) survey the body for cells expressing abnormal proteins, and kill them. These killer cells therefore have important roles protecting against virus infections and cancers; viruses produce their proteins inside infected cells, and cancers involve altered proteins that cause dysregulated cell growth. Cells in the body transport small pieces of the proteins inside them to display on their surface to allow CTLs to scan for abnormal proteins. All CTLs have unique receptors (T cell receptors, TCRs) on their surfaces that determine what they target, and if a receptor binds an abnormal protein on another cell, the CTL kills that cell. Thus each CTL varies in its targeting, and only a few may target any given abnormal virus or cancer protein. CTL successfully control many viral infections, often completely removing the virus, such as in influenza, or keeping the infection under chronic control so that it is not life threatening, such as in herpes. For HIV infection, CTLs are not as effective; while they delay the onset of AIDS, they ultimately fail to prevent it. The reason for this failure is not clear, but important factors are that there may be too few healthy CTLs with receptors against HIV, and that the virus mutates to avoid TCR binding. Our work takes advantage of recently discovered “broadly neutralizing antibodies” (bnAbs) that bind the HIV surface, at areas where HIV has difficulty mutating to avoid being bound. We use genetic engineering to create artificial TCRs using bnABs, called chimeric antigen receptors (CARs). Genes for CARs can be put into CTLs isolated from a person, re-targeting them against HIV, potentially creating lots of CTLs against HIV that the virus doesn’t mutate to escape. When these CARS are put into CTLs from healthy HIV-uninfected volunteers, the CTLs become active against virus-infected cells, killing them. These are candidates for gene therapy against HIV to boost the CTL response to control infection without drug treatment. Recently, CAR gene therapy has shown remarkable promise in the treatment of some cancers, providing proof-of-concept for this approach. Ironically, HIV was the first disease for which CAR gene therapy was tried in the late 1990s, but it was abandoned because the early CAR used likely had inadequate efficacy. Our design of new CARs offers new hope for revisiting this approach as a treatment for HIV infection, with the goal boosting the CTL response to control the virus and obviate the need for chronic drug treatment.

Scientific Abstract:
Although the use of chimeric antigen receptors (CARs) based on single-chain antibodies for gene immunotherapy of cancers is increasing due to promising recent results, the earliest CAR therapeutic trials were done for HIV-1 infection in the late 1990s. This approach utilized a CAR based on human CD4 as a binding domain and was abandoned for a lack of efficacy. The growing number of HIV-1 broadly neutralizing antibodies (BNAbs) offers the opportunity to generate novel CARs that may be more active and revisit this modality for HIV-1 immunotherapy. We used sequences from seven well-defined BNAbs varying in binding sites and generated single-chain-antibody-based CARs. These CARs included 10E8, 3BNC117, PG9, PGT126, PGT128, VRC01, and X5. Each novel CAR exhibited conformationally relevant expression on the surface of transduced cells, mediated specific proliferation and killing in response to HIV-1-infected cells, and conferred potent antiviral activity (reduction of viral replication in log10 units) to transduced CD8(+) T lymphocytes. The antiviral activity of these CARs was reproducible but varied according to the strain of virus. These findings indicated that BNAbs are excellent candidates for developing novel CARs to consider for the immunotherapeutic treatment of HIV-1. IMPORTANCE: While chimeric antigen receptors (CARs) using single-chain antibodies as binding domains are growing in popularity for gene immunotherapy of cancers, the earliest human trials of CARs were done for HIV-1 infection. However, those trials failed, and the approach was abandoned for HIV-1. The only tested CAR against HIV-1 was based on the use of CD4 as the binding domain. The growing availability of HIV-1 broadly neutralizing antibodies (BNAbs) affords the opportunity to revisit gene immunotherapy for HIV-1 using novel CARs based on single-chain antibodies. Here we construct and test a panel of seven novel CARs based on diverse BNAb types and show that all

these CARs are functional against HIV-1.

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