CALIFORNIA HIV/AIDS RESEARCH PROGRAM

Broadly neutralizing CARs for HIV therapy

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Current antiretroviral therapy is effective in controlling HIV/AIDS, but it does not cure a patient of the virus because the virus is able to lay dormant in a large reservoir of cells. In order to achieve a cure, it will be necessary to kill these virus-harboring cells. The body's natural mechanism to kill infected cells, cytotoxic T cells, may not be sufficient because dormant viruses have typically evolved mutations to escape detection by these cytotoxic T cells. Therefore, we propose to engineer T cells with broadly-neutralizing chimeric antigen receptors (bNAb-CARs). These bNAb-CARs will contain an antigen receptor that has been shown to recognize over 95% of HIV-1 strains, so we hypothesize that they will be effective in recognizing viral mutants. In addition, they contain several activation domains that will amplify the killer T cell response. These activation domains have been thoroughly tested in other disease models, such as B cell lymphomas, and clinical trials with B cell CARs have demonstrated long-lasting tumor remissions. We hypothesize that these bNAb-CARs will provide similar broad and durable protection from HIV expansion, and they may also be a mechanism through which to eliminate the viral reservoir. To test these hypotheses, we will produce bNAb-CARs in cell cultures and measure their ability to respond to and kill other cells that are either expressing some HIV-1 proteins or completely infected with replicating virus. We will also test these bNAb-CARs in a mouse model of HIV infection, in which humanized mice are infected with HIV-1 and then treated by transplantation of bNAb-CARs. If these bNAb-CARs are successful at controlling HIV infection in vitro and in vivo, we expect that this method can be translated in therapies in humans. Such a T cell therapy may lead to a new era of HIV/AIDS treatment in which patients do not need to depend on daily administration of antiretroviral drugs.

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