Reservoir Depletion Combined with ART for Functional Cure

Dennis Hartigan-O'Connor
University of California, Davis
Basic Biomedical Sciences
2014

Recent evidence shows that HIV "functional cure", if not eradication, is possible under some circumstances. 15 cases of functional cure after antiretroviral therapy (ART) have been reported and all share two characteristics: (i) early initiation and long duration of ART and (ii) very low residual viral DNA in long-lived $CD4^+$ T cells, a population that is widely acknowledged as an important viral reservoir. The 14 adult cases were characterized by very low HIV reservoir levels, particularly in long-lived $CD4^+$ T cell subsets, while the single pediatric case displayed even lower levels that were often undetectable. Indeed, the authors of the adult study concluded that achieving functional cure will "require reducing both the size and the distribution of HIV reservoirs, particularly among those resting $CD4^+$ T cells with a long lifespan." The goal of this project is to use monoclonal antibodies to dramatically reduce the lifespan of $CD4^+$ T cells in ART-treated model animals so that the size of the reservoir is reduced and functional cure is achievable.

Specifically, we plan to determine if $CD4^+$ T cell depletion by monoclonal antibodies facilities functional cure of infected animals. The animals will be infected with virus and ART initiated either two or five days later with a powerful, four-drug combination. The CD4-depleting antibody CD4R1 will be administered at days 1 and 15 following ART initiation in half of infected animals. ART will be discontinued after 60 days and parameters including viral load, immune response to virus, and presence of the virus in memory cell reservoirs assessed over time.

This interventional experiment tests directly the link between functional cure and lower infection of long-lived $CD4^+$ T cells that was observed in a previous study of adult post-treatment controllers. Although we will initiate treatment earlier than in those studies (five days vs. 1-2 months), the time point we have chosen is sufficiently late to allow detection of a peripheral viral RNA load and a reservoir-associated DNA load, while also being sufficiently early for cure under the right host conditions.