CALIFORNIA HIV/AIDS RESEARCH PROGRAM

Immunologic Pathways of HIV-1 Persistence

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Both human immunodeficiency virus (HIV) and human herpes virus infections persist lifelong. Almost all individuals infected with HIV are also co-infected with one or more human herpes virus, among which cytomegalovirus (CMV) is the most common.

Recent studies demonstrated that HIV-infected individuals experience frequent bursts of CMV replication and that these episodes (although mostly asymptomatic) are associated with increased inflammation and proliferation of T cells in blood. Presence of CMV replication has also been associated with a larger HIV DNA reservoir during suppressive antiretroviral therapy, but the mechanisms underlying these associations are still unclear.

This CHRP IDEA proposal was specifically designed to further investigate this complex relationship and to explore possible immunologic mechanisms connecting intermittent CMV reactivation and the size of the HIV DNA reservoir.

Our overarching hypothesis is that in HIV-infected persons receiving suppressive ART, bursts of CMV replication induces both host-derived and virus-derived IL-10, which then drives CD4 T cells to express PD-1. The expression of PD-1 then promotes persistence of replication-competent HIV in CD4 T cells. This hypothesis will be tested using innovative technologies (including droplet digital PCR, multicolor flow cytometry and viral induction assays) on unique well-characterized stored peripheral blood mononuclear cells (PBMCs) and genital secretions from 40 HIV-infected participants in the San Diego Primary Infection Consortium (SD-PIRC). Further, in collaboration with Drs. Vanpouille and Margolis (at the NIH) and using peripheral cells and human tissue cultures from healthy donors, we will explore exactly how CMV stimulates the expression of immune-modulatory molecules, like IL-10 and PD-1.

Based on recent observations, these connections are likely important, and could be a target of pharmacologic intervention. Such strategies could be important for both reducing the morbidity and mortality associated with HIV infection and for the design of future HIV eradication strategies.

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