IL-16 anti-HIV-1 therapy

To the editor — In the June issue of Nature Medicine, Zhou *et al.* raise the exciting possibility that stem cells from HIV-1 infected persons might be engineered to constitutively produce IL-16, creating an infectable population of CD4+ cells that would not support virus replication. The mechanism they hypothesize for their findings, suppression of mRNA expression, is similar to one previously described[2] where we demonstrated that rIL-16 repressed HIV-1 promoter activity up to 98% in a CD4-dependent fashion. Repression required sequences contained within the core enhancer but was not due to loss of a transcriptional activator protein. Rather, IL-16 appeared to induce a transcriptional repressor. Nanomolar concentrations of rIL-16, similar to the extracellular levels present in the experiments by Zhou *et al.*, repressed HIV-1 LTR-directed expression by 90%.

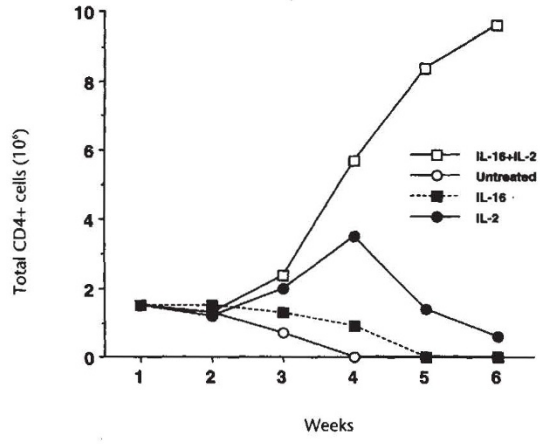

Fig. 1 Synergistic effect of IL-16 and IL-2 on CD4+ T cell proliferation. Human peripheral blood mononuclear cells (PBMC) obtained from an HIV-1-infected individual were cultured either as untreated or in the presence of IL-16 (10-10 M) or IL-2 (10 U/ml), or a combination of the two cytokines. The appropriate cultures received IL-16 once a week and/or IL-2 twice a week for up to 6 weeks. The number of CD4+ T cells were monitored weekly by FACS analysis, with 100% CD4+ T cells present by 6 weeks in cultures receiving IL-16 and IL-2.

Zhou *et al.* also found that virus entry is unaffected by IL-16, and that constitutive expression of the C-terminal 130 amino acids of IL-16 is sufficient to completely suppress virus replication. This is important because CD4+ T cells constitutively express IL-16 mRNA[3] and proIL-16 and release bioactive IL-16 upon activation (manuscript submitted). Since HIV-1 infects recently activated T cells, it appears that the production of IL-16 by these cells is insufficient to repress virus replication. This lack of effect may be because pretreatment with IL-16 is required to induce transcriptional repression[2]. The problems of delivery of IL-16 *in vivo* may be overcome by the engineered constitutive expression of IL-16 by CD4+ cells.

A few words of caution are appropriate, however. IL-16 has profound effects on CD4+ bone marrow precursors which might alter T or B cell maturation (pers. comm., Paul Szabo, Cornell Medical Center) and it is a potent proinflamatory cytokine with pleiotropic effects on T cell activation. Unregulated, constitutive secretion if IL-16 by bone marrow precursors might have adverse effects. However, there may be therapeutic potential for exogenous IL-16 administration, when dose could be controlled or discontinued.

Independent of its role in repressing HIV-1 replication, IL-16 may be effective in the selective immune reconstitution of CD4+ T cells from peripheral populations. IL-16 is a growth factor for CD4+ T cells, inducing IL2R expression and priming CD4+ T cells to proliferate in response to low concentrations of IL-2 (manuscript submitted). Treatment of PBMCs from HIV-1 infected individuals with IL-16 and IL-2 results in selective expansion of CD4+ T cells *in vitro* (see figure) and restores antigen specific proliferation. Thus, exogenous administration of IL-16 might have a dual effect of expanding functional peripheral blood CD4+ T cells while preventing virus replication in CD4+ T cells

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