ABSTRACTS

Oral Session I

Retrovirus Infections I

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New Opportunities for Gene Therapy Against HIV

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A major approach to the design of gene therapy for HIV-1 has been the creation of "dominant negative" mutants that do not themselves replicate efficiently but "out-compete" wild-type HIV-1 in the intracellular milieu. Previously described examples include p24 capsid mutants, polymerase mutants and matrix protein myristylation mutants. We designed two other classes of p17 matrix protein mutants. The first of these are deletion mutants with lesions in the region of amino acids (aa) 105-128. Such mutants allow virus assembly, but the virus made is defective in early viral DNA synthesis in subsequent infections. A second class of matrix mutants were designed with deletions of 10-15 aa in the regions of aa 10-41 and 78-104. Such mutants release virions that fail to incorporate the virus envelope, and thus lose infectiousness as a result. Another class of trans-dominant mutants were made by deleting regions of the transmembrane protein gene that encode the intracytoplasmic tail. These mutants also fail to incorporate envelope in the virus cores. These data clearly suggest that the cytoplasmic domain of HIV-1 gp41 interacts with the gag matrix protein for correct virus assembly. We also suggested another totally different approach using virus-specific interfering molecules (VSIM). As opposed to trans-dominant mutants, VSIM utilize the principle of viral packaging of a non-structural protein to interfere with subsequent replication. In this instance, we used the *vpx* gene of the HIV-2/simian immunodeficiency virus (SIV). This gene, not present in HIV-1, encodes a small peptide (p12) that is assembled with HIV-1 or HIV-2/SIV. When assembled with HIV-1 it inhibits the ability of released HIV-1 to subsequently infect new cells. Having evolved independently in the less virulent SIVs, the *vpx* gene is about 40% related to *vpr*, which is present in both HIV-1 and HIV-2/SIV. The products of both *vpx* and *vpr* are packaged into virions as nonstructural proteins. Finally, we recently demonstrated that interleukin 7 (IL-7) greatly facilitates the ability of cytotoxic T lymphocytes (CTL) from HIV-1 infected patients to kill autologous cells that express HIV-1 gp120. While most HIV-1 infected healthy carriers appear to have IL-7 inducible CD8+ CTLs, some do not. Those who lack IL-7 inducible CTLs also appear to lack expression of the IL-7 receptor (IL-7R) on CD8+ cells. In analogy with gene therapy with the IL-2 and TNF systems for melanoma, we propose that gene therapy be considered for selected HIV-infected individuals using the IL-7/IL-7R set of genes.