C46/CCR5/P140K Lentiviral Vector-transduced Autologous HSPCs

National Cancer Institute

Source

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Autologous CD34-positive, hematopoietic stem progenitor cells (HSPCs) genetically modified with a lentiviral vector expressing short hairpin RNA that targets human chemokine receptor 5 (CCR5) mRNA (shCCR5), the HIV entry inhibitor C46, a membrane-anchored 46-amino acid sequence found in HIV-1 gp41, and the drug resistance gene P140K, a mutant form of the DNA repair protein O6-methylguanine-DNA methyltransferase (MGMT), used to potentially provide resistance against human immunodeficiency virus (HIV) infection. Human autologous CD34+ HSPCs are isolated and transduced ex vivo with the pRSC-H1.shCCR5.Ubic.C46.EF1alpha.P140K.wpre lentiviral vector. shCCR5 binds to CCR5 mRNA and inhibits the expression of CCR5, a HIV-1 co-receptor that mediates HIV attachment and cell entry. Additionally, the expression of C46 blocks HIV-1 fusion to the cellular membrane. Upon re-infusion into the HIV-infected lymphoma patient, the C46/shCCR5/P140K lentiviral vector-transduced autologous HSPCs are resistant to HIV entry, which protects these cells against HIV infection and replication, and increases the amount of HIV-resistant CD4+ T-cells. HIV-resistant HSPCs could provide long-term protection against latent HIV infection and against HIV-associated cancers. In addition, the formation of immune cells resistant to HIV may result in the destruction of HIV-infected cells. P140K expression facilitates the in vivo chemoselection of gene-modified HSPCs, using O6-benzylguanine (O6BG)/bis-chloroethylnitrosourea (BCNU/carmustine), which increases the proportion of these HIV resistant CD34+ cells. P140K also protects these stem cells from future destruction by certain chemotherapeutic agents; if cancer were to develop, P140K is not inactivated by the MGMT inhibitor O6BG.