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Is gene therapy a good therapeutic approach for HIV-positive patients?

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Abstract

Despite advances and options available in gene therapy for HIV-1 infection, its application in the clinical setting has been challenging. Although published data from HIV-1 clinical trials show safety and proof of principle for gene therapy, positive clinical outcomes for infected patients have yet to be demonstrated. The cause for this slow progress may arise from the fact that HIV is a complex multi-organ system infection. There is uncertainty regarding the types of cells to target by gene therapy and there are issues regarding insufficient transduction of cells and long-term expression. This paper discusses state-of-the-art molecular approaches against HIV-1 and the application of these treatments in current and ongoing clinical trials.

Background

In 1983, a new virus was first isolated and associated with acquired immune deficiency syndrome (AIDS) [1]. Subsequently, scientists classified it as a *Lentivirus* belonging to the family *Retroviridae* and named it human immunodeficiency virus (HIV) [2]. HIV infection not only causes physical debility but also has negative social implications [3-7]. During the later stages of HIV infection, patients develop AIDS, presenting with severely depleted $CD4^+$ T-cell counts (<200 cells per microliter of blood) along with a myriad of opportunistic infections. According to the Joint United Nations Programme on HIV/AIDS, approximately 30 million people have lost their lives since the identification of the first AIDS patients in 1980. The global number of HIV-positive patients is around 39.5 million as of December 2006. There was an estimated average of 2.9 million deaths and 4.3 million new cases in 2006 [8].

Why consider gene therapy as a treatment modality?

Despite thousands of researchers worldwide working on a cure for HIV infection, none of the modalities have been completely successful. Currently, four classes of anti-retroviral drugs are available: nucleoside/nucleotide analogs, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, and fusion (or entry) inhibitors. These drugs, used in various combinations to treat HIV, form what is known as highly active antiretroviral therapy (HAART). However, HAART is expensive, has high toxicity rates, and must be administered lifelong, i.e. it is not curative. In addition to the above problems, the rate of emergence of resistant strains is high post-HAART. In studies conducted in the United States and Europe, over 50% of patients experienced virologic failure (viremia) while on antiretroviral therapy, and approximately 80% of these patients showed drug resistant HIV genotypes [9,10]. One long-term study found that by six years, approximately 80% of patients had their medications switched repeatedly due to drug resistance, resulting in an overall cumulative failure