negative) and the second twin as the recipient (HIV-positive). Lymphocytes from the donors were transduced to express a control gene (*neo* gene) or anti-HIV gene(s); a transdominant mutant Rev protein (TdRev) was used alone or with an anti-sense element directed against the HIV-1 TAR sequence on the same construct. Polymerase chain reaction demonstrated increased survival of modified lymphocytes in the initial weeks post-infusion in 9 of 10 recipients. In six of six recipients followed for approximately two years, T cells containing anti-HIV genes could be consistently detected and there was preferential survival of modified cells in one patient during a period of high HIV load [47].

Conclusion

Early promising results on the treatment of adenosine deaminase-severe combined immunodeficiency (ADA-SCID) by using gene therapy in the early 1990s [48] led the scientific community to apply the same principle to a host of other diseases, including HIV/AIDS. *In vitro* studies quickly demonstrated the feasibility of such approaches and preclinical and clinical trials were started later in the same decade. However, it was soon realized that a cure for HIV was far from easy. As many studies demonstrated, there were no serious adverse effects of the therapy, but neither was there any decrease of patients' viral loads. There was also the problem of transduction efficiency, and transduced cells had only transient expression of the transgene. Moreover, there was no consensus on target genes and methodology.

Despite some discouraging results from clinical trials, gene therapy for HIV is still a very promising approach. Scientists are already overcoming the problems of insufficient gene transduction by using novel constructs [49] or by switching to lentiviral-mediated transduction [50,51]. The first clinical trial using lentiviral vectors in HIV-positive patients began in 2001, and results will be forthcoming [52]. The recent clinical studies by Podsakoff *et al*. and Morgan *et al*. in 2005 support the hypothesis that anti-HIV genes confer a survival advantage to modified lymphocytes [40,47], especially under conditions of high HIV titers, thus offering a potential benefit to infected individuals.

Other promising strategies for the near future include the use of siRNAs and fusion proteins to deliver these molecules [53-55]. Early HIV regulatory genes like *tat* and *rev* could be susceptible targets for siRNA because genes encoding late structural proteins are dependent on Tat and Rev protein expression [56]. Scherer *et al*. showed that *tat*- and *rev*-specific siRNAs were more effective at inhibiting HIV-1 replication than multiple siRNAs targeting *env* [57]. Other research groups have demonstrated success *in vitro* by targeting Gag or HIV receptors with siRNA [58,59]. Song *et al*. (2005) took advantage of the nucleic acid binding properties of protamine and fused it to the heavy chain Fab fragment of an anti-HIV Env antibody to deliver siRNA to HIV-infected cells [54].

According to von Laer *et al*. (2006), antiviral genes that inhibit the processes of reverse transcription and integration potentially offer significant therapeutic benefit [60]. They based their prediction on mathematical models, which analyzed the effects of genetically modified T cells on viral replication and T cell kinetics. This strategy could include targeting cellular factors involved in these enzymatic processes. Developing siRNAs that target reverse transcriptase and integrase genes themselves have potential to be effective anti-HIV therapies. Although these genes code for late protein products, inhibition of these genes could create defective virus particles incapable of initiating subsequent replication cycles.

While the initial achievements using siRNA against HIV have employed transient expression systems, stable systems have been reported and offer hope for long-term efficacy [30,53,61-65]. The specificity of siRNAs reduces the potential side effects of gene therapy but, on the other hand, it increases the possibility of making a virus partially or completely resistant to siRNA with the slightest mutation [66-69]. The strategy of simultaneously targeting several conserved regions of HIV using multiple different siRNAs could potentially overcome this problem of viral escape.

In conclusion, gene therapy is a very attractive method for treating HIV-positive patients. The approaches undertaken so far have yielded encouraging results from a safety efficacy standpoint. Future efforts should focus on improving transduction efficiencies and long-term expression and on optimizing cellular targets in order to achieve the desired therapeutic benefits, which include decreasing viral loads, increasing or sustaining high $CD4^+$ T cell counts, and improving immune function in HIV-infected individuals.

Competing interests

The author(s) declare that they have no competing interests.

Authors' contributions

JGM and DPW produced the manuscript together. Both authors read and approved the final manuscript.

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