

# Abstract

GENETIC MODIFICATION OF STEM CELLS FOR THE THERAPY OF INHERITED DISEASES.



Stem cell transplantation is an established therapeutic approach in cancer therapy and tissue replacement. Genetic modification of stem cells opens entirely new perspectives for the treatment a variety of genetic disorders of blood and epithelial cells. On the long term, transplantation of genetically modified stem cells might impact on the therapy of diseases of wider social interest, such as muscular dystrophy, cystic fibrosis, neurodegenerative disorders and diabetes. Genetic manipulation requires sophisticated tools to insert, or replace, genes into the human genome. For over two decades, vectors derived from retroviruses provided a simple and efficient tool to deliver, and integrate, genes into human stem cells for clinical application. Pioneer studies have demonstrated the potential of these vectors for the treatment of immunodeficiency and skin diseases, but raised serious safety concerns due to uncontrolled insertion into the target cell genome and interference with normal gene regulation. Several years of close genetic analysis of the interaction between retroviral vectors and the human genome have provided a wealth of information that now allow the design of safer and more efficient tools for gene transfer into stem cells. Research of new gene transfer tools allowing targeted integration or homologous recombination is also under way, and might lead to the development of much safer vectors in a near future. At the moment, however, there is little alternative to the use of vectors derived from animal or human (HIV) retroviruses. Since transplantation of genetically corrected stem cells has proven its efficacy in several diseases with little or no therapeutic alternative, finding a sensible balance between risks and benefit is the only way to meet a medical need and continue a technological development that might eventually solve all problems. All therapies have side effects, and the medical community has learned how to deal with them in decades of practice. Genetic manipulation should not be considered an exception.