

Gene Therapy for congenital and acquired disorders: promoting the progress of clinical applications

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The concept of correcting genetic diseases by inserting genes into human stem and progenitor cells for therapeutic purposes emerged with the initial understanding of the molecular basis of genetic diseases. With more than 6000 human genetic diseases caused by a mutation in a single gene resulting in a disorder that can be inherited through generations, the initial clinical applications of gene therapy for these disorders were hailed - in the early '90s- as potentially the fourth great revolution of medicine. However, despite the development of different vectors for specific applications and numerous convincing results in proof-of-concept studies based on animal models for genetic disease, clinical efficacy was slow to come. It took more than a decade to witness the first unequivocal evidence that gene transfer into hematopoietic stem cells could cure different variants of congenital immunodeficiencies. The following years accumulated important additional progress in the treatment of genetic diseases of the blood, the skin, the eye and the nervous system. Furthermore, expansion of these applications to gene transfer-based treatments of hematologic malignancies also proved successful. In particular, we developed efficacious gene transfer strategies to control graft-versus-host disease and to provide fast and efficacious immune reconstitution in the context of mis-matched transplants for leukemia. This approach may provide a suitable donor to all patients candidate for a hematopoietic stem cell transplant but lacking an HLA-identical donor. This technology progressed through phase II into phase III trials, becoming one of the most advanced gene therapy approach in clinical development.

Based on these important results, further progress can be expected. However, for this to occur at a faster pace, issues related to the safety of the vector, the nature of the target cell and organ, and the gene transfer procedure utilized will have to be balanced against the expected clinical benefit. Finally, strategies for cost containment of the development process for therapies that –in many circumstances- may be limited to a very small number of patients affected by a rare genetic disorder must become a priority for all parties involved.