GENE THERAPY FOR INHERITED BLOOD DISEASES, FROM VIRAL VECTORS TO GENE EDITING

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Twenty-five years ago, genetically modified bone marrow cells were administered for the first time to a child suffering from adenosine deaminase (ADA) deficiency, a rare disorder of the immune system. Since then, gene therapy has struggled to find its place in clinical medicine, amid a rollercoaster of successes and setbacks and hype and skepticism with little precedent in modern times. Recently, a series of authoritative clinical studies proved that transplantation of genetically modified hematopoietic stem cells can cure severe diseases like immunodeficiencies, hemoglobinopathies and metabolic diseases, contributing to transforming gene therapy into one of the hottest area of investment for the biotechnology and the pharma industry. The basic technology for the genetic modification of stem cells relies on retroviral vectors, and particularly on those derived from oncoretroviruses or lentiviruses, such as HIV-1. Integration of these vectors in the genome may, however, have undesired effects caused by insertional deregulation of gene expression at the transcriptional or post-transcriptional level. The occurrence of severe adverse events in several clinical trials involving the transplantation of stem cells genetically corrected with retroviral vectors showed that insertional mutagenesis is not just a theoretical event, and that retroviral transgenesis is associated with a finite risk of genotoxicity. Addressing these issues brought new basic knowledge on virus-host interactions and on the biology and dynamics of human somatic stem cells. More recently, a new generation of technology emerged, aimed at correcting the genome rather than replacing defective gene function. This technology relies on designer nucleases capable of generating double- or single-stranded breaks in genomic DNA, which are then repaired either by error-prone non homologous end-joining or by the more precise homologous recombination. This allows generating knock-out mutations or repairing genes with remarkable precision and efficiency in many cell types. At Genethon, we are using lentiviral vector technology to correct Wiskott-Aldrich syndrome, X-linked SCID, chronic granulomatous disease and sickle-cell disease, while developing CRISPR/Cas9-based genome editing for a number of applications.