Gene Therapy of Hemoglobin Disorders

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Gene therapy of hemoglobin disorders is especially challenging given the requirements for massive haemoglobin production, specifically in erythroblasts, and the lack of selective advantage for corrected hematopoietic progenitors. Compound β^E/β° thalassemia is the most frequent form of severe thalassemia in Southeast Asian countries and their diaspora. The β^E-globin allele bears a point mutation that causes alternative splicing. The abnormally spliced RNA is not coding a globin chain, whereas the correct mRNA expresses a mutated β^E globin inducing instability of HbE upon oxidation. Approximately half of the β^E/β° thalassemia patients are transfusion dependent. The only curative therapy is allogeneic hematopoietic cell transplantation, but only a minority of patients has an HLA-matched familial donor and those who do still risk rejection or graft-versus-host disease.

Here we show that 3.4 years after lentiviral β-globin gene transfer, an adult patient with severe β^E/β° thalassemia, dependent on monthly transfusions since childhood, has become transfusion independent for the last 2.4 years. Blood haemoglobin is stably maintained between 9 and 10 g/dL-1, of which one-third contains vector encoded therapeutic globin. Part of the therapeutic benefit results from a partial dominant cell clone, in which the vector causes transcriptional activation of HMGA2 in erythroid cells with increase level of a truncated HMGA2 mRNA, insensitive to degradation by let-7 microRNAs. This clone, that accompanies therapeutic efficacy, may be coincidental and stochastic or results from hitherto benign cell expansion caused by the dysregulation of the HMGA2 gene in stem-myeloid progenitor cells (Cavazzana-Calvo et al. Nature 2010; 467; 318-23). Extension of the trial and complementary or alternative approaches to increase safety or efficacy will be discussed.