

Sickle cell anemia is characterized by repeated vascular occlusions and hemolysis, primarily resulting from the sickle-shaped RBCs formed under hypoxia. Treatment for the disease is largely symptomatic. Bone marrow transplantation, a curative modality, is limited to a few with matched donors and has potential side effects. Increasing the expression of the anti-sickling gamma-globin in the RBCs by long term administration of hydroxyurea reduces the frequency of sickling events. Gene therapy using the gamma-globin gene in hematopoietic stem cells (HSCs) can improve the survival of RBCs derived from the genetically modified HSCs permanently. Gene therapy for hemoglobinopathies with onco-retroviral vectors has suffered from problems of vector instability, low titers and variable expression. With the advent of better vectors, improved gene transfer techniques and a better understanding of stem cell and vector biology, gene therapy is going from the bench to the bedside in disorders like SCID and hemophilia B. The recently developed lentiviral vectors transduce the non-dividing HSCs and stably export large genomic fragments required for high-level regulated globin gene expression. Self-inactivating (SIN) lentiviral vectors are even more advantageous: the viral long terminal repeat is deleted upon integration into cells, completely inactivating viral transcription, a feature ideal for the expression of a highly lineage-restricted gene and, additionally, improves the bio-safety. We have recently shown remarkably lineage-specific and long-term expression of GFP and a therapeutic correction of the murine erythropoietic porphyria in primary and secondary mice with SIN-lentiviral vectors. We would like to extend these results and examine the properties of SIN-lentiviral vectors in carrying the human gamma-globin gene and erythroid regulatory elements for gene transfer into HSCs, resulting in high-level expression of gamma-globin in RBCs.