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Targeted integration at alpha-globin locus in human hematopoietic stem and progenitor cells

?-thalassemia is a devastating blood disorder caused by mutations in the HBB gene encoding ?-globin, where treatment involves lifelong, costly management of the resulting lack of hemoglobin and hemolytic anemia. In addition to the shortage of ?-globin, the accumulation of ?-globin is also a significant contributor to disease pathology, driven by expression from two highly homologous genes, HBA1 and HBA2.

Stanford researchers have optimized a CRISPR/Cas9-based gene editing technique to replace one of the two genes encoding ?-globin with a functional version of HBB. Despite the similarity of the HBA1 and HBA2 genes, the inventors have developed highly selective CRISPR guide sequences that can specifically knock-in the HBB gene into the HBA1 locus, leaving the HBA2 gene intact. The resulting gene expression profile produces a normalized ratio of ?-globin and ?-globin to restore functional hemoglobin.

Researchers demonstrate that hematopoietic stem cells can be edited efficiently to replace HBA1 with HBB, and successfully engraft and reconstitute in a mouse model to restore hemoglobin levels. Due to the redundancy of alpha-globin genes and the fact that site-specific integration at the HBA1 locus achieves a red blood cell-specific expression profile of custom transgenes, this technology has broad clinical application outside of thalassemia.

Ongoing Research
Researchers find that in patient-derived cells they were able to: 1) efficiently edit HSPCs; 2) normalize the ratio of beta-globin:alpha-globin; 3) restore functional hemoglobin; and 4) successfully engraft edited cells into mice.

Applications

- Treatment of alpha and beta thalassemia
- Treatment of monogenic blood disorders
- Harnessing red blood cells as a therapeutic delivery vehicle via integration of a therapeutic gene into the HBA1 locus

Advantages

- Potential one-time treatment for a chronic blood disorder
- Effective independent of patients' mutation profile
- Does not rely on expression of fetal hemoglobin, which may not be maintained indefinitely in adults
- Does not use a lentiviral vector, negating risk of random integration
- Autologous treatment approach has low risk of immune rejection of transplanted hematopoietic stem cells
- No requirement for matched bone marrow donor

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