Docket #: S21-377

Red blood cell-specific transgene expression for treating genetic enzyme deficiencies

Stanford researchers have developed a new gene editing approach that enables red blood cell-specific gene expression for the treatment of enzyme deficiencies.

Available protein-based enzyme replacement therapies are not curative, require frequent infusions, and often become less effective over time. Similarly, emerging strategies that use a viral vector to deliver a functional copy of the defective gene to the liver are limited by pre-existing neutralizing antibodies, potentially life-threatening immune responses, and a decline in enzyme production over time.

Researchers therefore developed a new strategy in which red blood cells are turned into enzyme-producing factories, taking advantage of the fact that red blood cells are produced in large numbers and circulate throughout the body. To achieve red blood cell specific gene expression, researchers use *ex vivo* CRISPR/Cas editing of hematopoietic stem cells to insert a functional copy of the enzyme behind a promoter (HBA1 or HBA2) that is only active in red blood cells. Scientists further optimized this strategy for the treatment of hemophilia B, caused by mutations in factor IX. They increased the amount of factor IX secreted into the bloodstream by over 3-fold and engineered the protein to be 3.3-fold more active.

Stage of development
Animal data: treatment of phenylalanine hydroxylase deficiency and hemophilia B in mice

Applications

- Treatment of intracellular enzyme deficiencies, *e.g.* phenylketonuria
- Treatment of extracellular enzyme deficiencies, *e.g.* hemophilia A and B

Advantages

- One-time cure
- Redundancy of HBA1 and HBA2 means that red blood cell function is not affected
- Red blood cell specific gene expression prevents effects on other blood cell function
- Approach is agnostic to specific genetic mutations
- Minimal risk of insertional mutagenesis
- Avoids immune response associated with *in vivo* therapies
- Effective even at low levels of engraftment, allowing for minimally toxic conditioning
- Improved factor IX secretion (3-fold)
- Improved factor IX activity (3.3-fold over Padua variant currently used in clinical trials)

Patents

- Published Application: WO2023224992
- Published Application: 20250312488

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