Docket #: S19-501C

Composition of the Treatment of X-linked Chronic Granulomatous Disease (X-CGD) Deficiency in Human Hematopoietic Stem and Progenitor Cells (HSPCs)

Genome editing of human hematopoietic stem and progenitor cells (HSPCs) has the potential to create a new class of medication for the treatment of inherited and acquired genetic diseases of the blood and immune system. Researchers at Stanford have optimized a genome editing method in HSPCs using CRISPR/Cas9 in combination with AAV6-medicated homologous recombination (HR). The Cas9 nuclease and a short guide RNA (sgRNA) were delivered to the target genomic sequence. The double-stranded DNA break made by Cas9 was repaired by HR with a designed donor DNA template in the AAV6 vector that contains the desired genetic modification. Using this new method, researchers were able to achieve highly efficient editing, where both single nucleotide and several kilobases of DNA can be changed.
The researchers have applied the method to monogenic diseases, and have developed sgRNA and AAV6 donor DNA sequences that work well in HSPCs for several severe combined immunodeficiency disorders (SCID), including X-linked Chronic Granulomatous Disease (X-CGD) Deficiency.

Applications

- **Gene editing** for treatment of X-linked Chronic Granulomatous Disease (X-CGD) Deficiency
- **Therapeutic delivery**: Safe harbor approach in human CCR5 locus constitutes a flexible platform for delivering therapeutic proteins for other disorders (e.g.

metabolic diseases)

Advantages

- **Novel**: No existing treatment available for X-linked Chronic Granulomatous Disease (X-CGD) Deficiency
- **High frequency of success**: Genome editing frequencies in human HSPCs higher than previously reported
- **High specificity and safe**: No evidence of abnormal hematopoiesis following transplantation and minimal off-target activity and toxicity were observed
- **Flexibility**: From single nucleotide up to several thousand bases can be modified ex vivo or in vivo

Publications

- *For other similar disease indications with related method*:
  - Pavel-Dinu M, Porteus MH, et al. (2019). Gene correction for SCID-X1 in long-term hematopoietic stem cells. *Nat Commun*. PMID: 30967552; PMCID: PMC6456568.
  - Porteus MH, et al. (2019). Human genome-edited hematopoietic stem cells phenotypically correct Mucopolysaccharidosis type I. *Nat Commun*. 10(1):4045. PMID: 31492863; PMCID: PMC6731271.

Patents

- Published Application: WO2022081585
- Published Application: 20230357798

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