Docket #: S21-197

Correction of polycythemia vera via CRISPR/AAV6 genome editing

Polycythemia vera is a rare blood cancer characterized by the hyperproliferation of red blood cells, leading to coagulation events like strokes and heart attacks. There are no curative treatments available, only symptom management in the form of treatments with suboptimal side effect profiles.

The condition is caused by a mutation in the JAK2 gene, which could be corrected via a gene editing strategy. However, a gene editing approach remains challenging due to the need to retain activity from the wild type JAK2 allele for normal hematopoiesis. Further, the mutant site needs to be edited with near perfect efficiency to prevent the eventual expansion of the proliferative mutant populations.

Inventors at Stanford's Porteus lab have developed a CRISPR-based method in hematopoietic stem cells (HSCs) to deactivate the JAK2 mutation most frequently altered in polycythemia vera and related myeloproliferative neoplasms (MPNs). Using a system that incorporates two guide RNAs, the inventors were able to develop a targeting method to limit insertions and deletions in exons of the wild type allele, while the mutant sequence can be specifically targeted for nuclease activity. The mutant gene is then repaired via homologous recombination, with the normal donor template delivered in an AAV6 capsid.

In in vitro experiments using human doner hematopoietic stem cells, the gene editing technique produced efficient replacement of the mutant JAK2 allele, with minimal impact on the wild type allele. Edited cells can subsequently be used as a starting material for autologous bone marrow transplant.

Stage of development
In vitro proof of concept in patient-derived HSCs, in vivo research ongoing.

Applications

- Potentially curative therapeutic for polycythemia vera or other JAK2-mutated MPNs
- Ex vivo gene editing strategy for incorporation into stem cell transplantation protocols

Advantages

- Potential for one-time, curative treatment option

Patents

- Published Application: WO2023060059
- Published Application: 20240382528

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