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VIEW ON NEWS

CRISPR comes of age: A fairytale turned into bedside reality?

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Abstract We devote this short piece to highlight one recent article published in ***Cell Stem Cell***, reporting the correction of large chromosomal inversions of the factor VIII (*F8*) gene in cells from Hemophilia A patients using the CRISPR-Cas9 technology, one of the first attempts to edit large segments of chromosomes in patient cells using such methodology. The corrected cells were found free of off-target mutations and producing functional factor VIII in hemophilia mouse model. This work heralds another major advance in bringing CRISPR closer to the therapeutic reality.

Precision genome editing using the CRISPR (Clustered Regions of Interspersed Palindromic Repeats) endonuclease technology has started to come of age. With its ever-improving specificity, the initial clinical safety concerns regarding off-target genetic mutations have been tapering off. Medical science has never been so close to realizing the dream of correcting gene mutations, the culprits of many inheritable diseases, with pinpoint precision. The advent of CRISPR technology greatly enhanced the feasibility of finding cures for untreatable genetic diseases in the not-so-distant future.[1] Added to the parade of successful proof-of-principle experiments is a recent ***Cell Stem Cell*** article by Park, et al, reporting the correction of large chromosomal inversions in the factor VIII (*F8*) gene in cells from Hemophilia A patients using the CRISPR-Cas9 technology.[2] In this study, the authors first generated induced pluripotent stem cell (iPSC) clones from the patients' somatic cells and subsequently corrected the chromosomal inversions of the *F8* gene, one of the first attempts to edit large segments of chromosomes in patient cells using the CRISPR-Cas9 methodology. The authors did not detect any off-target mutations among the chromosomally corrected iPSC clones using whole-genome and targeted deep sequencing, suggesting that the risk of unintended gene alterations was kept minimal. Endothelial cells (a major source of plasma coagulation factor VIII in normal subjects) were derived from the corrected iPSC clones. By transplanting these corrected endothelial cells into a mouse model of lethal hemophilia, the authors were able to demonstrate *in vivo* restoration of the plasma factor VIII activity, which was correlated with a shortened bleeding time, as well as prolonged survival. However, it remains unknown how long these corrected endothelial cells last in the animals after injection, and it is unclear whether these cells actually engraft in the mouse vascular vessels so that the cure can be considered permanent. In order to sustain long-term efficacy, the corrected cells must be engrafted into the patient's tissues or organs, which is difficult to achieve due to the extremely low engrafting efficiency of certain types of cells, including those of the endothelial lineage. Despite these hurdles, this newly reported benchmark success represents another major step forward in bringing this CRISPR-tale closer to a bedside reality.

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Conflicts of interest

The authors declare no conflicts of interest.

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Fei Li, Executive Associate Editor *
The Editorial Office of Genes & Diseases, Chongqing 400046, China

Jim Hu
Department of Pathology and Laboratory Medicine, The Hospital for Sick Children, University of Toronto, Toronto, Ontario M5G 0A4, Canada

**Corresponding author.*
E-mail address: fei@genesndiseases.org (F. Li)

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