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Curing Sickle Cell Anemia by Genomic Edition of Induced Stem Cells

Bio Science & Technology
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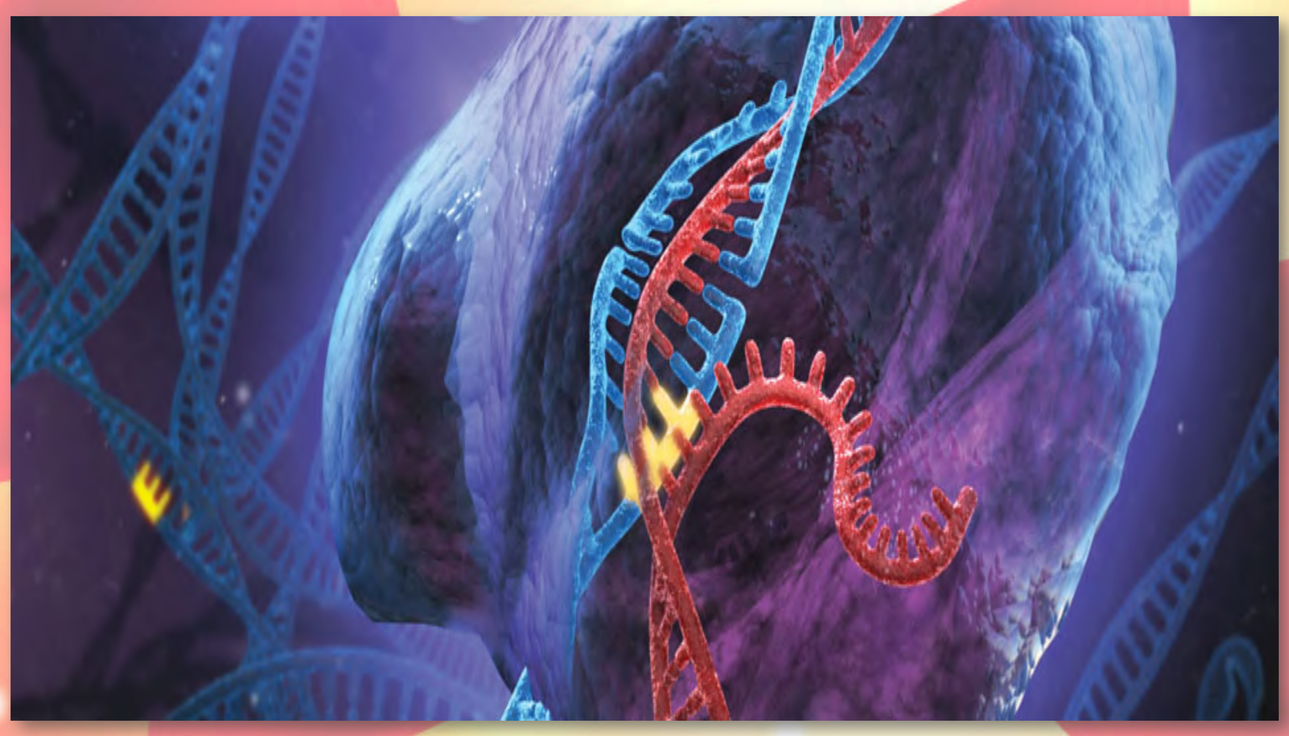
Abstract

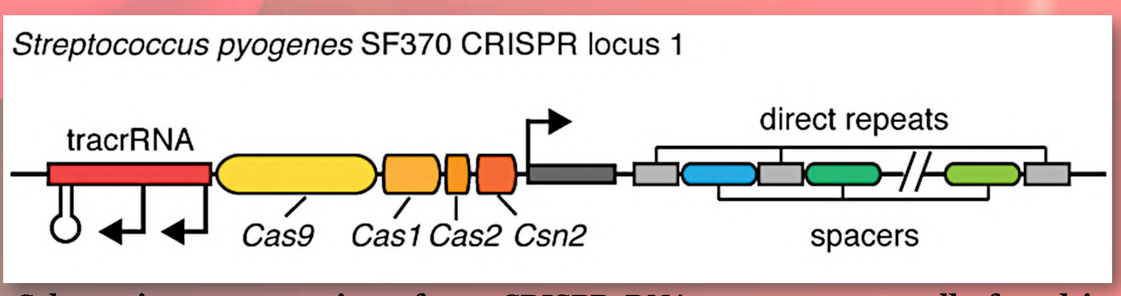
Sickle cell anemia is a genetic disease affecting hundreds of millions of people worldwide. It causes abnormal red blood cells resulting in acute pain episodes and other severe symptoms. The project focuses on correcting the mutation by genome editing. The proposed method involves transplanting cured stem cells into the bone marrow of the patient. The goal is to create an effective life-long solution in order to improve the quality of life and decrease the mortality rate in affected populations.

Introduction

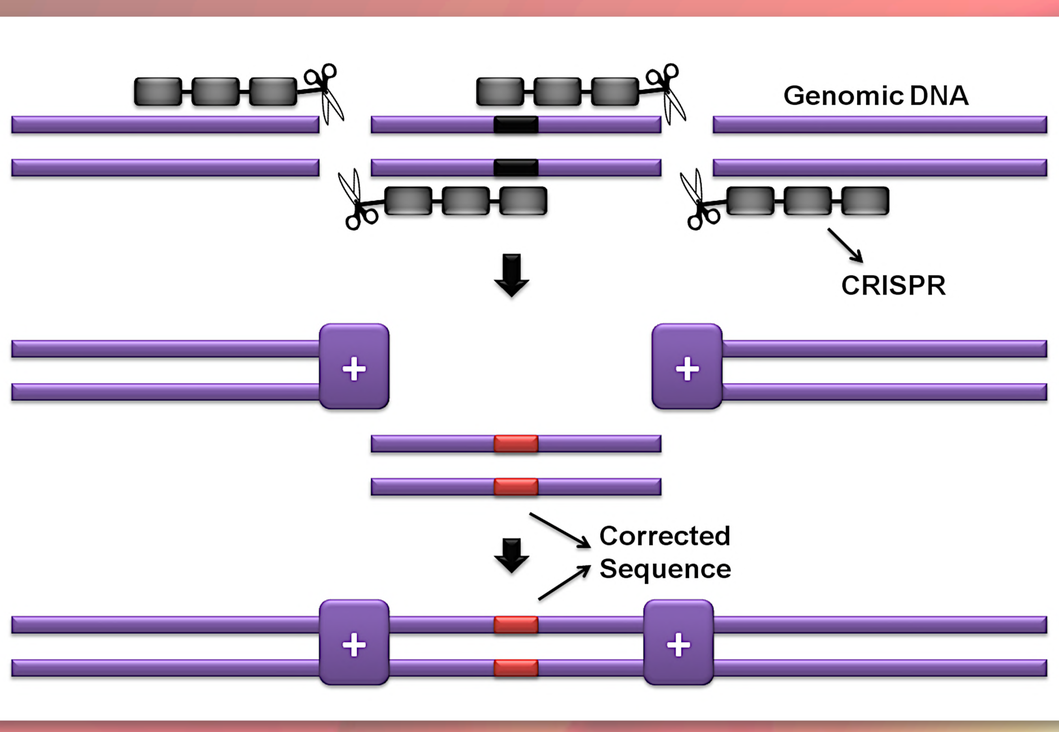
Sickle cell anemia is an autosomal recessive genetic disease in which red blood cells become sickle-shaped. It is caused by a single base substitution in the β-globin gene, which is located on the short arm of chromosome 11. As a result, valine is produced instead of glutamic acid causing the production of sickle hemoglobin (HbS). This results in the formation of a distorted shape of the erythrocytes. Due to this abnormal shape, small blood vessels can be blocked, causing serious damage to the bone, spleen and skin tissues. This may lead to episodes of pain, frequent infections, hand-foot syndrome or even multiple organ failure. The distorted erythrocytes are also more susceptible to hemolysis, which leads to serious anemia.[1,2]



Artistic rendering of the CRISPR/Cas9 genomic edition system
Source: http://www.genome-engineering.org/crispr/



Schematic representation of one CRISPR DNA sequence naturally found in bacteria, which produces the Cas9 protein and RNA guide. For genomic edition, a different, synthetic version is used.
Source: http://www.genome-engineering.org/crispr/?page_id=27



Approximative representation of the CRISPR/Cas9 system which is used for genomic edition. The inserted template includes the correction of the mutation.

Methods

Our research is focused on creating a permanent treatment for sickle cell anemia via a genetic correction of the mutation and transplantation of corrected blood stem cells to the patient's bone marrow. Firstly, blood cells are collected from the patient. The cells are turned into Hematopoietic Stem Cells (HSCs), stem cells of the blood - via a newly discovered method using viruses to introduce certain proteins into the cell. The HSCs can give rise to all other blood cells, therefore the correction of the mutation in HSCs will result in the life-long production of healthy blood cells.[3]

To correct the induced stem cells, the CRISPR/Cas9 system is used. This system allows the specific editing of the cell's genome by cutting its DNA and then letting it repair itself. The Cas9 protein is inserted and directed by a RNA guide to the mutated point and then it cuts the DNA at that point. Simultaneously, a healthy version of the sequence is inserted. This sequence is used by the cell's own repair system to fix the induced cut. In this way, the CRISPR/Cas9 allows the correction of the mutation in the previously obtained stem cellsBefore transplantation of the stem cells, the success of the correction is tested using a restriction site.[4,5,6]

Ethical Questions

Although promising, our proposed method raises some ethical concerns regarding potential risks of unwanted effects of the treatment. Further research is necessary to completely dismiss the possible harmful effects, and assess and improve the economical accessibility of the treatment in the less privileged populations.

Backround source: http://www.biosciencetechnology.com/news/2013/07/stem-cell-gene-therapy-sickle-cell-disease-advances-toward-clinical-trials

References

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2) University of Michigan aHealth System http://www.med.umich.edu/digitallab/m2pathlabs/hemepath/pdf%20files/pictoral%20review%20sickle%20cell%20anemia.pdf (Accessed 5.6.2014)

3) Riddell, Jonah et al. 2014 Reprogramming Committed Murine Blood Cells to Induced Hematopoietic Stem Cells with Defined Factors. Cell 157(3):549-564.

4) Kim, Hyongbum and Kim, Jin-Soo. 2014 A guide to genome engineering with programmable nucleases. Nature Reviews Genetics 15:321–334.

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6) Balboa, Diego and Weltner, Jere. Uni. of Helsinki (personal communication).