**[CRISPR-Cas9 as TDT and SCD treatment]**

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Stem cell, transcription factors, mesenchymal, stem cell therapy,CRISPR-Cas9

**Abstract: Monogenic diseases such as sickle cell and Beta thalassemia have affected millions across the globe. A study directed by the CRISPR therapeutics and Vertex Pharmaceuticals utilized the CRISPR-Cas9 technique to genetically edit out BCL11A erythroid enhancer gene locus present in sickle cell affected blood. Similarly, CRISPR-Cas9 was used to target Transfusion – dependent Beta thalassemia of donated blood samples. Genetically altered blood, specifically CD34+ cells were introduced into patients carrying the diseases. The results following one year of study showed bone marrow and blood allelic changes in which the BCL11A gene was no longer in production by the patient’s own body.**

**Introduction**

The use of the newly developed clustered regularly interspaced short palindromic repeats or CRISPR-Cas9 has allowed for the hijacking of the body’s immune response and allowed for the ability to genetically copy DNA sequences. These advances in technology allow for the specific editing of the universal genetic language that holds the blueprints for every living thing on earth. This technique has brought forth the expansion of genetic disease treatment in revolutionary technical terms. Research of the treatment of two specific monogenic diseases; Sickle cell disease affecting some reported 300,000 and Transfusion dependent Beta thalassemia affecting a reported 60,000 patients a year, has progressed. Transfusion dependent Beta-thalassemia are often the result of mutations present in the hemoglobin Beta subunit gene that cause reduced erythropoiesis. Sickle cell disease is the result of point mutations in the hemoglobin Beta subunit gene that are noted to replace the glutamic acid with valine. These mutations occur at position 6 of the amino acid chain, and is responsible for abnormalities in erythrocytes, possible organ damage and episodic vaso-occulive responses. Current treatments of said diseases are restricted to transfusional type therapies along with iron chelation in patients suffering from Transfusion dependent Beta-thalassemia. Treatment of sickle cell disease is similarly treated with multiple blood infusions and hydroxyurea. Bone marrow transplantation has often been successfully used to treat both sickle cell disease and transfusion dependent Beta-thalassemia but the low rate of eligible leukocyte antigen receptive donors makes widespread treatment unsustainable due to compatibility issues. Diagnosis of previous diseases often manifests following the first year of birth in patients. The offset time of illness is due to the presence of fetal hemoglobin present in humans following parturition. The presence of fetal hemoglobin is responsible for the regulation of Y-globin located in the BCL11A zinc receptor locus of the second human chromosome has been noted as a primary substrate in reducing the effects of said diseases in patients, hence the asymptomatic response of children before the age of 1.

**Recent Progress**

Trials conducted under the funding of the CRISPR Therapeutics and Vertex Pharmaceuticals selected two candidates among multiple patients dealing with Beta hemoglobin disease as well as Sickle cell disease respectively. Both candidates were selected from a large group of patients dealing with said diseases for an extended period of time. Both patients had received multiple blood transfusions throughout their treatment phase and were therefore selected for the study. The patient with transfusion dependent beta-thalassemia disease was a female of 19 years. The patient chosen with sickle cell disease was a 33-year-old female with a prevalent history of treatment and side effects. Both patients were treated with a blood infusion. The blood infused was altered using CRISPR-Cas9 gene editing to alter the red blood cells at the BCL11A genomic point. This allowed the altered cells to act as Progenitor cells for the individual, with the hope that the patients body would begin generation of said fixed cells. Both patients were directed to 15 transfusion over a year long treatment term.

**New Results**

The usage of modified red blood cells in treatments of both studies resulted in significant grafting of T cells and red blood cells to the bone marrow of both experimental groups. Bone marrow grafts signified that T and red blood cell development might be taken in by the patients blood supply. Patient blood draws spaced three months apart revealed significant levels of allelic editing present and subsequent production of hematopoietic stem cells which was expected. No off-target gene editing was identified in each experimental group present giving prudence to the accuracy of the genetic edits. Both studies correlated with each other in maintaining neutrophil and platelet engraftment, hence the red blood cell types were accepted by the bodies marrow. Levels of fetal hemoglobin present in both patients were maintained at a high frequency during the collection timetable. Follow-up treatments of six other patients followed after the study, each with similar results derived from the treatments. Every following experimental group reported adverse effects including pneumonia and nonserious lymphopenia. In each case, and whether the transfusion directly correlated to the adverse effects is not known. All adverse effects were treated and resolved during the study.

**Discussion**

The usage of CRISPR-Cas9 to directly modulate red blood cells for transfusion purposes in treatments of sickle cell disease and transfusion dependent Beta thalassemia has yielded exciting results in genomic patient treatment. The ability of a host body to accept said altered red blood cells and properly use them in a successful grafting procedure has allowed for patients of the study to naturally continue to produce fetus hemoglobin. This allowed subjects to be able to reduce the expression of Y globin synthesis. The results of cell editing treatment in genomic blood disease has proven to have successful results in real-world-testing but further long-term sample collection and analysis are required to corroborate as well as support the effectiveness of said techniques for future use.

**References**

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