A Treatment For Beta-thalassemia via High-Efficiency Targeted Genome Editing of Hematopoietic Stem Cells

Grant Type: Strategic Partnership II
Grant Number: SP2-06902

Reporting Period: Year 1

Summary of progress Our CIRM-funded effort aims to develop a treatment for beta-thalassemia. Beta-thalassemia is an inherited genetic disorder that is caused by mutations (changes in the DNA) in a gene called beta-globin. This gene produces a protein that forms hemoglobin in red blood cells that carry oxygen to the body. In an individual with beta-thalassemia, beta-globin is not produced (or is made in dramatically reduced quantities), and so the person does not make enough healthy red blood cells. The treatment, which is essential for life in these patients, is repeated blood transfusions (typically once a month or more frequently). The transfusion of blood this frequently results in a dangerous condition called “iron overload,” which must be treated with costly drugs. In general, the quality of life of many people with beta-thalassemia is poor. At present, there is only one cure, and that is to carry out a bone marrow transplant. This involves taking special cells from a healthy person called “hematopoietic stem cells” that give rise to blood cells for the whole of a person's life, and giving them to the patient so that they that they are now able to make healthy red blood cells for their lifetime. However, the cell donor must be an immunologic match to the patient and for many people with beta-thalassemia, such donors are not available. Our approach to treating beta-thalassemia aims to genetically engineer a person’s hematopoietic stem cells (change the DNA inside the cell) to allow them to make healthy red blood cells using a technology that we have developed called “zinc finger nucleases,” or ZFNs. We plan to obtain stem cells from a beta-thalassemia patient, genetically engineer them by transiently exposing them to ZFNs, and then transplant them back into the same individual, making the patient their own donor. The genetic engineering is designed to replicate a situation observed in certain people with beta-thalassemia who have milder symptoms than others. Such patients have a much higher than average level of a “backup” form of beta-globin, called fetal globin, in their blood. All people make fetal globin while in utero and after birth, but in infancy the levels of fetal globin decrease and the child begins to make adult beta-globin. It is at this stage that the symptoms of beta-thalassemia become evident. However, if person with beta-thalassemia has high level of fetal globin, they will be spared the severe effects of the disease. We know that certain individuals who have an elevated level of fetal globin do so because they have a less active form of a gene called BCL11A that normally shuts down the production of fetal globin during infancy. Making use of this observation, our approach is to knock out BCL11A in a patient’s own stem cells, transplant them back into the patient to allow the production of fetal hemoglobin and, as a consequence, increase production of healthy red blood cells. In order to test drugs in humans investigators must consult with the US Federal Drug Administration (FDA) and ultimately submit data about the investigational drug to various regulatory bodies including the FDA as part of Investigational New Drug (IND) application. This past year, we held a meeting with the Center for Biologics Evaluation and Research of the FDA known as a “pre-IND” and received useful guidance on issues that we should address in preparing the IND filing. We also presented our program to the Recombinant DNA Advisory Committee of the NIH (RAC); our proposed preclinical safety assessment program and plan for the phase I clinical trial received unanimous approval from the RAC. Our work this year focused on two major deliverables that are necessary to achieve the goal of beginning a clinical trial of our approach. The first one relates to our ability to purify and efficiently genetically engineer a sufficient quantity of stem cells from a patient with beta-thalassemia. Working with healthy volunteers, and in a setting that is identical to the one we plan to use during our clinical trial, we have been able to consistently obtain sufficient quantities of hematopoietic stem cells to treat an individual with beta-thalassemia, and attain high levels of targeted genetic engineering in those cells. As part of a preclinical safety assessment program, we have initiated and completed a series of studies to determine whether the genetic engineering we perform has any unforeseen untoward consequences in the cell. When we have completed this effort, we aim to file the IND application with the FDA before the end of the year and, pending FDA acceptance, initiate the phase 1 clinical trial in 2015.
Objective of the study is to develop an autologous stem cell gene therapy for Beta Thalassemia. Team developed a zinc-finger nuclease genome editing strategy for beta-Thalassemia designed to specifically knock out the gene encoding the BCL 11A transcription factor. Objective of the study included completion of the IND-enabling studies, filing of an IND and conduct of a Phase 1 clinical trial.

Investigator:

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<tr>
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Disease Focus: Blood Disorders, Pediatrics

Human Stem Cell Use: Adult Stem Cell

Award Value: $2,760,540

Status: Closed

Application Title: A Treatment For Beta-thalassemia via High-Efficiency Targeted Genome Editing of Hematopoietic Stem Cells

Public Abstract: β-thalassemia is a genetic disease caused by diverse mutations of the β-globin gene that lead to profoundly reduced red blood cell (RBC) development. The unmet medical need in transfusion-dependent β-thalassemia is significant, with life expectancy of only ~30-50 years despite standard of care treatment of chronic blood transfusions and iron chelation therapy. Cardiomyopathy due to iron overload is the major cause of mortality, but iron-overload induced multiorgan dysfunction, blood-borne infections, and other disease complications impose a significant physical, psychosocial and economic impact on patients and families. An allogeneic bone marrow transplant (BMT) is curative. However, this therapy is limited due to the scarcity of HLA-matched related donors (<20%) combined with the significant risk of graft-versus-host disease (GvHD) after successful transplantation of allogeneic cells.

During infancy, gamma-globin-containing fetal hemoglobin protects β-thalassemia patients from developing disease symptoms until gamma globin is replaced by adult-type β-globin chains. The proposed therapeutic intervention combines the benefits of re-activating the gamma globin gene with the curative potential of BMT, but without the toxicities associated with acute and chronic immunosuppression and GvHD. We hypothesize that harvesting hematopoietic stem and progenitor cells (HSPCs) from a patient with β-thalassemia, using genome editing to permanently re-activate the gamma globin gene, and returning these edited HSPCs to the patient could provide transfusion independence or greatly reduce the need for chronic blood transfusions, thus decreasing the morbidity and mortality associated with iron overload. The use of a patient’s own cells avoids the need for acute and chronic immunosuppression, as there would be no risk of GvHD. Moreover, due to the self-renewing capacity of HSPCs, we anticipate a lifelong correction of this severe monogenic disease.
Statement of Benefit to California:

Our proposed treatment for transfusion dependent \(\beta\)-thalassemia will benefit patients in the state by offering them a significant improvement over current standard of care. \(\beta\)-thalassemia is a genetic disease caused by diverse mutations of the \(\beta\)-globin gene that lead to profoundly reduced red blood cell (RBC) development and survival resulting in the need for chronic lifelong blood transfusions, iron chelation therapy, and important pathological sequelae (e.g., endocrinopathies, cardiomyopathies, multiorgan dysfunction, bloodborne infections, and psychosocial/economic impact). Incidence is estimated at 1 in 100,000 in the US, but is more common in the state of California (incidence estimated at 1 in 55,000 births) due to immigration patterns within the State. While there are estimated to be about 1,000-2,000 \(\beta\)-thalassemia patients in the US, one of our proposed clinical trial sites has the largest thalassemia program in the Western United States, with a population approaching 300 patients. Thus, the state of California stands to benefit disproportionately compared to other states from our proposed treatment for transfusion dependent \(\beta\)-thalassemia.

An allogeneic bone marrow transplant (BMT) is curative for \(\beta\)-thalassemia, but limited by the scarcity of HLA-matched related donors (<20%) combined with the significant risk of graft-versus-host disease (GvHD) after successful transplantation of allogeneic cells. Our approach is to genetically engineer the patient’s own stem cells and thus (i) solve the logistical challenge of finding an appropriate donor, as the patient now becomes his/her own donor; and (ii) make use of autologous cells abrogating the risk of GvHD and need for acute and chronic immunosuppression.

Our approach offers a compelling pharmacoeconomic benefit to the State of California and its citizens. A lifetime of chronic blood transfusions and iron chelation therapy leads to a significant cost burden; despite this, the prognosis for a transfusion dependent \(\beta\)-thalassemia patient is still dire, with life expectancy of only ~30-50 years. Our proposed one-time treatment aims to reduce or eliminate the need for costly chronic blood transfusions and iron chelation therapy, while potentially improving the clinical benefit to patients, including the morbidity and mortality associated with transfusion-induced iron overload.

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