Pre-clinical development of gene correction therapy of hematopoietic stem cells for SCID-X1

Grant Award Details

Pre-clinical development of gene correction therapy of hematopoietic stem cells for SCID-X1

Grant Type: Preclinical Development Awards

Grant Number: PC1-08111

Project Objective: The final developmental candidate will be Autologous Gene Corrected CD34 Cells at the IL2RG Gene ("AGC-CD34/IL2RG") and will consist of of autologous HSPCs from patients with SCID-X1 that have been genetically corrected using homologous recombination mediated genome editing. We expect that our pre-clinical development may modify these parameters in some fashion our planned final cell product will be delivered to SCID-X1 subjects as an intravenous infusion and will have the following characteristics: Total CD34+ dose=>2 x 10e6cells/kg; Gene Correction Efficiency >1%; Translocation Frequency <10-5.

Investigator:

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Institution:	Stanford University
Type:	PI

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Name:	Maria-Grazia Roncarolo
Institution:	Stanford University
Type:	Co-PI

Disease Focus: Blood Disorders, Genetic Disorder, Immune Disease, Pediatrics, Severe Combined Immunodeficiency, X-linked (X-SCID)

Human Stem Cell Use: Adult Stem Cell

Award Value: $874,877

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Grant Application Details

Application Title: Pre-clinical development of gene correction therapy of hematopoietic stem cells for SCID-X1

Public Abstract: Severe combined immunodeficiency caused by mutations in the IL2RG gene on the x-chromosome (SCID-X1 or "bubble boy disease") is a devastating genetic disease that results in boys not being able to form an immune system. If they are exposed to the environment for even a short period of time they can get infections that a normal immune system would eliminate without problems but instead can be lethal. While in the past the only treatment for this disease was to keep the boys protected from the environment by being isolated in a bubble, hence its colloquial name, now we treat SCID-X1 with allogeneic bone marrow transplantation (allo-BMT). In allo-BMT the defective immune system of the patient is replaced by the functional immune system of the donor. Allo-BMT now saves the life of 70-95% of patients depending on where the donor immune system comes from and how sick the patient is before receiving the transplant. There remain, however, significant limitations to allo-BMT. These include that in some patients the new immune system is still not as good as a normal immune system, thus keeping the patient at risk for lethal infections, and toxicity from the new immune system causing a reaction in which the donor immune system sees the patient as "foreign" and attacks the tissues causing graft vs host disease. In rare patients, however, a single stem or progenitor cell that gives rise to the immune system will have a spontaneous mutation that reverts the disease causing DNA sequence back into a non-disease causing sequence thereby correcting the gene. The goal of this program is to develop a specific gene correction procedure that could be applied to almost every patient with SCID-X1 rather than to it naturally occur in an extremely rare lucky few.

Towards this end we have developed a system in which we make a specific break in the IL2RG gene. This break activates the cell to repair the break and we can take advantage of the cell fixing the break to insert a good copy of the gene at the site of the break. In this way, we utilize the cell's own repair machinery to fix the gene. We have shown that we can do gene repair in human blood stem and progenitor cells from anyone and create corrected cells thousands of corrected stem and progenitor cells rather than just a single cell rarely occurs naturally. We have shown that these modified cells can create blood cells, including immune cells. The goal of this specific project is to further improve the gene correction system by optimizing the different components, to assure that the gene correction system is safe and does not cause deleterious effects in the blood stem and progenitor cells, to scale the process up to a size that would be needed to treat a patient and to perform the regulatory tasks that are needed to bring what would be a first-in-human gene correction approach to patients.

Statement of Benefit to California:	SCID-X1 is a rare disease that only affects a handful of patients in the state of California each year. Finding a genetic cure based on gene correction, therefore, might seem not to be of great benefit to the state of California or its citizens, This would be a mistaken impression for several reasons. For the handful of patient's and families that are affected that are affected every year, dealing with the disease will be among the most challenging life events they will ever face and finding a gene correction cure would be of tremendous, life-changing benefit to them. Moreover, t's significance far outstrips its incidence because of its notoriety as the "bubble boy disease" and the recognition that it is a seminal proof-of-concept genetic disease. That is, if one can figure out how to genetically correct stem cells to cure SCID-X1 then that provides the foundation for a strategy to genetically correct stem cells that cause a multitude of other genetic diseases. That is, a pipeline for gene correction for all children with genetic diseases in California will be started. As succinctly summarized by the head of research and development of a large international pharmaceutical company "One will get you a hundred." While the medical benefits of first curing SCID-X1 and then curing other genetic diseases is clear, the financial ramifications of turning chronic lifelong genetic diseases that directly cost society sometimes millions of dollars per patient per lifetime and indirectly cost society even more into acute diseases that can be cured with one procedure are enormous. Finally, California attracts the best and the brightest from all over the world because it is known as a place where transformative, innovative, and impactful discoveries are made and supported. When we are successful with this definitive and innovative approach to curing a genetic disease, it will continue to re-affirm the seminal importance of California and its citizens in making the world a better place.

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