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Experimental gene therapy may improve health outcomes for patients with some forms of blood disorders

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New research adds to a growing body of evidence that gene therapy, an experimental technique that involves correcting or replacing a person's mutated or malfunctioning genes, may improve health outcomes for patients with inherited bleeding and immune disorders as well as some forms of blood cancer. Studies showcasing these advances will be presented today at the 57th American Society of Hematology (ASH) Annual Meeting and Exposition.

Patients with severe blood diseases may have no other therapeutic options but to depend on life-long blood transfusions or a stem cell transplant. For these patients, experimental gene therapies have demonstrated promise in improving outcomes and even curing diseases with otherwise grim prognoses. While past efforts were associated with toxicities and susceptibility to treatment-associated leukemia – in some cases the treatment being worse than the illness – pioneering hematologists have made great progress in correcting these issues. As a result, current methods have demonstrated improved safety and long-term efficacy in treating a number of diseases.

Research presented today shows the continued promise of lentiviral gene therapy, an approach in which healthy genetic material is delivered to a cell via a non-communicable virus. One study shares follow-up data on patients who can forgo blood transfusion after receiving lentiviral gene therapy to treat beta-thalassemia. Another two studies demonstrate the promise of gene therapy using a lentiviral vector to rebuild the immune systems of patients who suffer from two rare blood diseases, Wiskott-Aldrich Syndrome and severe combined immunodeficiency (SCID-X1), also known as "Bubble Boy disease." A fourth study to be presented today presents an exciting first clinical trial using engineered donor immune cells to prevent progressive cancer after stem cell transplant. Finally, a late-breaking study demonstrates promising early outcomes of a first-in-human trial using a patient's own genetically modified immune cells to eradicate multiple myeloma.

"The research presented today pertains to some of the most severe and hard-to-treat blood diseases, which have a devastating impact on patients and families, and until now could not be effectively treated or cured," said George Daley, MD, PhD, Boston Children's Hospital. "We are encouraged by the results and advances in the field of gene therapy, which appears to be effective in a range of conditions."

This press conference will take place on Saturday, December 5, 2015, at 7:30 a.m. in Room W208AB of the Orange County Convention Center.

Gene Therapy for Patients with Severe Beta-Thalassemia May Reduce or Eliminate Life-Long Need for Blood Transfusions
Update of Results from the Northstar Study (HGB-204): A Phase I/II Study of Gene Therapy for Beta-Thalassemia Major via Transplantation of Autologous Hematopoietic Stem Cells Transduced Ex-Vivo with a Lentiviral Beta AT87Q-Globin Vector (LentiGlobin BB305 Drug Product) [201]

- Beta-thalassemia is a blood disorder caused by a mutation in the *HBB* gene and characterized by reduced production of the protein hemoglobin, which affects the blood's ability to transport oxygen and is associated with life-threatening complications such as severe anemia and organ damage.
- Patients with more severe forms of beta-thalassemia require frequent blood transfusions to replace their unhealthy blood with healthy blood. However, transfusion-related complications such as iron overload can be deadly.
- To provide an alternative to life-long transfusions, researchers developed LentiGlobin BB305, which uses a non-communicable virus to deliver a fully functioning *HBB* gene to a patient's own blood-producing stem cells. Researchers hypothesized that hemoglobin production from the modified stem cells might reduce or eliminate the need for blood transfusions in patients with beta-thalassemia major.
- This Phase I/II study examined if using LentiGlobin BB305 to introduce a fully functioning hemoglobin gene into a patient's stem cells was a safe and effective treatment. Investigators collected stem cells from transfusion-dependent beta-thalassemia major patients, inserted the healthy gene, and then infused the cells back into the patient after first giving high-dose chemotherapy to destroy the thalassemia-producing

blood cells.

- As of October 28, 13 transfusion-dependent beta-thalassemia major patients received LentiGlobin BB305 therapy. The modified gene is in all patients and producing the corrected hemoglobin. Of the nine patients who were treated more than six months ago, five are transfusion-free, including three patients treated longer than a year ago. These five all have *HBB* gene mutations that are associated with reduced, but not totally absent, production of functional hemoglobin.
- The other four patients have had transfusion needs reduced but not entirely eliminated. These four patients have two copies of a specific type of *HBB* gene mutation known as beta 0 and appear to need a higher level of corrected hemoglobin to reliably eliminate the RBC transfusions. However, all patients demonstrated a reduction in transfusion volume ranging from 33 percent to 100 percent. Two serious adverse events, skin infection and veno-occlusive liver disease, have been reported during the study but were not related to treatment with the genetically modified cells.
- These results indicate that gene therapy is a promising option for reducing or eliminating blood transfusions and limiting long-term complications in patients with this disease.

Mark C. Walters, MD, UCSF Benioff Children's Hospital, Oakland, Calif., will present this study during an oral presentation on Sunday, December 6, at 8:00 a.m. in room Tangerine 3 (WF3-4), level 2 of the Orange County Convention Center.

Up to Five-Year Follow-Up of Gene Therapy in Patients with Rare Immune Disease Shows Continued Improved Clinical Outcomes

Safety and Clinical Benefit of Lentiviral Hematopoietic Stem Cell Gene Therapy for Wiskott-Aldrich Syndrome [259]

- Wiskott-Aldrich Syndrome (WAS) is a rare genetic disease of the immune system characterized by low platelet counts, recurrent infections, easy bruising, bleeding, eczema, autoimmune disorders, and high susceptibility to cancer. The disease is caused by a mutation in the *WAS* gene.
- Stem cell transplant is the most effective treatment for WAS but is associated with potentially life-threatening complications, particularly in the absence of matched donors.
- This Phase I/II clinical trial, initiated in April 2010, examined whether engineering patients' own stem cells with the correct *WAS* gene could directly improve the severe complications associated with this disease.
- Researchers extracted blood-forming stem cells from patients with a mutated *WAS* gene and used a lentiviral vector to engineer the cells to express the normal form of *WAS*.
- As of October 2015, eight patients have been treated at a median age of 2.2 years. All patients were alive after a median follow up of 3.3 years after treatment (range: 0.1 – 5.4 years). No adverse reactions to gene therapy were observed after infusion.
- Notably, six patients with a follow-up period of more than two years after receiving treatment experienced a marked reduction in the rate of severe infections and bleeding events after treatment, as compared with before gene therapy.
- While continued patient follow-up is needed to understand the long-term safety and efficacy of this treatment, this form of gene therapy appears to be well tolerated and may lead to sustained clinical benefit for these patients.

Francesca Ferrua, MD, San Raffaele Telethon Institute for Gene Therapy (TIGET), San Raffaele Scientific Institute, Milan, Italy, will present this study during an oral presentation on Sunday, December 6, at 12:00 noon in room W230, level 2 of the Orange County Convention Center.

Study Presents Evidence That Gene Therapy Can Rebuild Immune System in Children, Adolescents and Young Adults With Rare Immunodeficiency

Lentiviral Hematopoietic Stem Cell Gene Therapy for Older Patients with X-Linked Severe Combined Immunodeficiency [261]

- X-linked severe combined immunodeficiency (SCID-X1), also known as "Bubble Boy disease," is a rare, inherited disorder of the immune system affecting almost exclusively males. SCID-X1 is caused by mutations in the *IL2RG* gene. Boys with SCID-X1 are born with poorly functioning immune systems and are prone to life-threatening infections.
- The treatment of choice for infants with SCID-X1 is a stem cell transplant from a matched sibling donor. For

infants without a matched sibling donor, use of partially matched stem cells from a parent without using pre-transplant conditioning with chemotherapy to assist engraftment is lifesaving but only partially restores their immune system, improving T cell immunity but not correcting B and natural killer (NK) immune cell functions. These patients require life-long treatment with immune globulin, a complex mix of antibodies derived from donated blood plasma.

- Researchers sought to demonstrate that a combination of gene therapy to insert a normal form of the *IL2RG* gene into patients' own stem cells and use of low-dose marrow conditioning to enhance engraftment of the patients' own gene-corrected stem cells would successfully restore both B cell immunity and antibody production.
- Study participants included five patients 23, 24, 7, 16, and 10 years of age with worsening immune systems and complex medical problems despite one or more previous transplants from a partially matched parental donor. Patients have been treated with follow-up periods of three months to three years.
- Researchers extracted blood-forming stem cells from the patients and delivered a normal *IL2RG* gene to the cells using a lentiviral vector. The stem cells were infused back into the patients after a low dose of busulfan chemotherapy marrow conditioning.
- The two older patients with significantly longer follow-up demonstrated increasing percent of immune cells with corrected genes, specifically T cells (13-55%), B-cells (38%), and NK cells (56-76%), and restoration of antibody production.
- This is the first study of gene therapy in older SCID-X1 patients, including those well into late adolescence and early adult stages of life demonstrating broad restoration of immunity that includes full restoration of antibody production. Results demonstrate that this approach can salvage failed stem cell transplants by rebuilding the immune system.

Suk See De Ravin, MD, PhD, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Md., will present this study during an oral presentation on Sunday, December 6, at 12:30 p.m. in room W230, level 2 of the Orange County Convention Center.

Engineered Donor T Cells May Eradicate Progressive Disease After Stem Cell Transplant
Allogeneic T-Cells Expressing an Anti-CD19 Chimeric Antigen Receptor Cause Remissions of B-Cell Malignancies after Allogeneic Hematopoietic Stem Cell Transplantation without Causing Graft-Versus-Host Disease [99]

- Stem cell transplant, a form of cell replacement therapy in which the diseased stem cells are replaced with healthy donor cells, is a potential curative therapy for patients with treatment-resistant blood cancers.
- Progressive disease is a leading cause of death after stem cell transplant. If a patient's cancer continues to spread after transplant, the current standard treatment is to infuse the patient with unmanipulated donor white blood cells to fight the disease. However, this procedure is often ineffective and increases risk of graft-versus-host disease (GVHD), a complication that occurs when the new cells attack the patient's body.
- Instead of unmanipulated white blood cells, researchers hypothesized that an infusion of genetically engineered donor T cells would eradicate progressive disease after stem cell transplant in patients with B-cell malignancies, which include types of leukemia and non-Hodgkin lymphoma.
- Researchers conducted a clinical trial in which donor T cells were engineered to express a chimeric antigen receptor (CAR). CAR T cells are programmed to first recognize CD19, a protein on the surface of most B-cells, and then attack the targeted cell.
- Patients who experienced resurgence of B-cell malignancies after stem cell transplant received a single infusion of CAR T cells obtained from each recipient's stem cell donor. No chemotherapy or other therapies were administered.
- Eight of the 20 total patients obtained remissions, including six complete remissions and two partial remissions. Response rates were highest for patients with acute lymphocytic leukemia, with four of five patients achieving complete remission.
- The longest ongoing complete remission is more than 30 months in a patient with chronic lymphocytic leukemia.
- No patient developed GVHD after infusion with CAR T cells.
- The findings support the hypothesis that infusing anti-CD19 donor CAR T cells is a promising method for treating B-cell malignancies that emerge after stem cell transplant.

James N. Kochenderfer, MD, Center for Cancer Research, National Cancer Institute, Bethesda, Md., will present this

study during an oral presentation on Saturday, December 5, at 12:30 p.m. in room W314, level 3 of the Orange County Convention Center.

First-in-Human Trial Using Engineered Cells to Target Multiple Myeloma Shows Early Promise
Remissions of Multiple Myeloma during a First-in-Humans Clinical Trial of T Cells Expressing an Anti-B-Cell Maturation Antigen Chimeric Antigen Receptor [LBA-1]

- Multiple myeloma (MM) is a cancer of the plasma cells. The disease is incurable in most cases and new therapies are urgently needed.
- The B-cell maturation antigen (BCMA) is a protein expressed by both normal and malignant plasma cells. Because BCMA is only expressed by plasma cells and a small fraction of B-cells, it is a promising target for treating multiple myeloma.
- In this Phase I clinical trial, researchers extracted immune T cells from patients and genetically engineered the cells to express an anti-BCMA chimeric antigen receptor (CAR-BCMA) to recognize and kill the myeloma cells. Patients received one round of chemotherapy before their own engineered cells were infused back into their bodies at one of four dose levels.
- As of November 2015, 11 patients with advanced MM and a median of seven previous failed therapies have participated in the trial.
- One month following infusion, the two patients treated at the highest dose level demonstrated the strongest anti-cancer responses. One patient achieved a stringent complete remission at two months following the CAR-BCMA T cell infusion. The other patient had undetectable myeloma in the bone marrow plasma cells but has not yet reached complete remission status.
- Of the six patients treated on the lowest two dose levels, one patient experienced a short partial remission of two weeks and the other five remained stable, their disease neither improving nor worsening.
- Two patients on the second-highest dose level maintained stable disease, and one patient obtained a very good partial response.
- Toxicity and side effects were mild for patients who received the lowest dose levels. Patients who received the highest doses experienced cytokine release syndrome, a severe and potentially fatal side effect of therapy characterized by high fever, muscle pain, and heart and kidney problems.
- Engineered CAR-BCMA T cells were detected in the blood of all 10 patients assessed to date. Toxicities were similar to those observed in leukemia patients treated with similar therapies.
- These findings suggest that CAR-BCMA is a promising option for advanced multiple myeloma patients who have failed several previous therapies.

James N. Kochenderfer, MD, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Md., will present this study during the Late-Breaking Abstracts Session on Tuesday, December 8, at 7:30 a.m. in Hall D, level 2 of the Orange County Convention Center.

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