# Lentiviral gene transfer improves human alpha globin production for the treatment of alpha thalassemia

July 2 2024

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Researchers at Children's Hospital of Philadelphia (CHOP) and the University of Pennsylvania Perelman School of Medicine have pioneered a new model that offers a potential platform for developing novel therapies to treat alpha thalassemia (AT), a severe blood disorder.

The findings were published in the journal *Blood*.

Thousands of children are born with AT every year, especially in South-East Asia, India, the Middle East, and the Mediterranean basin. When functioning normally, the genetic trait may provide protection against malaria and result in mild anemia. However, when both parents are carriers of faulty genes, children face an elevated risk of severe AT.

In the most severe cases, the disease can be fatal without in utero intervention. Children with severe AT often require ongoing blood transfusions and extensive medical care.

"New treatments for blood disorders have experienced remarkable success in recent years, particularly for conditions like beta thalassemia and sickle cell disease. However, despite representing a growing health care challenge, alpha thalassemia has drawn significantly less attention," said senior author Stefano Rivella, Ph.D., a research faculty member in the Division of Hematology at CHOP.

"Our hope is that generating animal models will provide a powerful tool for future research, along with avenues of investigation for human patients."

Allogeneic bone marrow transplantation (BMT) is currently the only available therapeutic option for patients with severe AT, and that method also requires an appropriate donor. Additionally, until now, research into therapeutic advancements for AT was limited due in part to the challenge of creating adult mouse models with this disease.

In this study, researchers designed an innovative model by deleting alpha globin genes in adult mice using a lipid nanoparticle (LNP) embedded within mRNA that induced the deletion of the alpha globin genes. This led to the production of faulty red blood cells (RBC) with abnormal

hemoglobin, called HbH, that binds oxygen tightly, preventing its delivery to tissues and causing paradoxical hypoxia.

The targeted LNP platform technology was previously established by Hamideh Parhiz, PharmD, Ph.D., a co-senior study author and Assistant Professor of Medicine at Penn Medicine. Her team also generated targeted LNP to hematopoietic stem cells encapsulating mRNA for the current study.

Once the alpha globin genes were deleted, the mice experienced decreased oxygen levels comparable to individuals with severe AT. The mice were flooded with RBC that couldn't transport oxygen, posing an extreme health threat. The researchers confirmed that this model can now be applied to test novel or genetic therapies in human patients to improve their clinical care.

Rivella, along with members of his lab, including, Laura Breda, Ph.D., Maxwell Chapell, Ph.D., Lucas Tricoli, Ph.D., and Amaliris Guerra, Ph.D., developed a method to perform gene complementation to repair the defective genetic traits via hematopoietic stem cell modification and transplantation.

The researchers used a lentiviral vector expressing human alpha globin, named ALS20∝I, and found it produced high levels of human alpha globin in the mice, sustaining them and boosting normal hemoglobin production. They also noted that ongoing bone marrow transplantation resulted in the continued expression of human alpha globin, indicating that ALS20∝I effectively modifies stem cells in the blood to provide long-lasting corrections to AT.

"This innovative approach represents a much-needed step forward in the treatment of alpha thalassemia," said Rivella. "We look forward to further research and the promise of improved patient outcomes with

fewer complications over time."

**More information:** Maxwell Elliott Chappell et al, Use of HSC Targeted LNP to Generate a Mouse Model of Lethal α-Thalassemia and Treatment via Lentiviral Gene Therapy, *Blood Journal* (2024). DOI: 10.1182/blood.2023023349

Provided by Children's Hospital of Philadelphia