Researchers develop proof-of-concept treatment that elevates adult and fetal hemoglobin

June 1 2021

Stefano Rivella, Ph.D., Kwame Ohene-Frempong Chair on Sickle Cell Anemia and Professor of Pediatrics at CHOP. Credit: CHOP

Researchers at Children's Hospital of Philadelphia (CHOP) have

developed a proof-of-concept treatment for blood disorders like sickle cell disease and beta-thalassemia that could raise hemoglobin levels by activating production of both fetal and adult hemoglobin. Using a viral vector engineered to reactivate fetal hemoglobin production, suppress mutant hemoglobin, and supply functional adult hemoglobin, the researchers developed an approach that could produce more hemoglobin through a single vector. The results were published in *Haematologica*.

"Until now, researchers have been exploring one of two approaches to treating blood disorders like sickle cell disease or beta-thalassemia: adding a functional copy of the adult hemoglobin gene, or increasing production of fetal hemoglobin," said senior author Stefano Rivella, Ph.D., Kwame Ohene-Frempong Chair on Sickle Cell Anemia and Professor of Pediatrics at CHOP. "In this study, we have done both simultaneously, which provides an opportunity to produce more hemoglobin per vector in these patients."

Sickle cell disease and beta-thalassemia are genetic blood disorders caused by errors in the genes for hemoglobin, a protein that is found in red blood cells and carries oxygen from the lungs to tissues throughout the body. In utero, the gamma-globin gene produces fetal hemoglobin, but after birth, this gene is switched off and the beta-globin gene is turned on, producing adult hemoglobin. Patients with sickle cell disease and beta-thalassemia have mutations in the beta-globin gene, which leads to mutant hemoglobin production and, as a consequence, serious health complications, ranging from delayed growth and jaundice to pain crises, pulmonary hypertension, and stroke.

Current research has focused on treating these blood disorders by either increasing fetal hemoglobin, which is not mutated in these conditions, or adding back a functional copy of adult hemoglobin via gene therapy, using an engineered vehicle known as a viral vector to supply new genetic material. However, there are limitations to both of these

approaches, and neither has been established as a fully curative approach.

In order to increase hemoglobin levels in one therapy, the researchers—led by co-first authors Danuta Jarocha, Ph.D. and Silvia Lourenco, Ph.D. - combined the two tactics into a single gene therapy vector. To do so, they focused on a transcription factor called BCL11A, which effectively operates the switch that turns off the production of fetal hemoglobin and turns on the production of adult hemoglobin. The researchers hypothesized that if they could use an engineered vector to repress BCL11A, which would keep fetal hemoglobin production turned on and turn off the production of mutant adult hemoglobin, while also adding back a functional copy of the beta-globin gene, they could induce greater hemoglobin production.

Working in cell lines of patients with sickle cell disease and beta-thalassemia, the researchers tested their vector—which included a gene coding for adult hemoglobin and a microRNA sequence that would target BCL11A—and found that the vector was able to elevate fetal and adult hemoglobin simultaneously in vitro. Although BCL11A was not completely knocked down, the suppression was sufficient to reduce production of the mutant adult hemoglobin. By elevating both fetal and functional adult hemoglobin, the vector was able to induce more functional hemoglobin production than that of a vector expressing beta-globin alone.

"Future studies will evaluate this approach using an even stronger vector that we developed in our lab and published on recently," Rivella said. "Combining these two technologies, we hope to make an even more powerful vector that can provide curative levels of hemoglobin to these patients."

This research was supported by the CuRED Frontier Program at CHOP,

which is dedicated to finding new and improved curative therapies for blood disorders like sickle cell disease and beta-thalassemia.

More information: Silvia Pires Lourenco et al, Inclusion of a shRNA targeting BCL11A into a β-globin expressing vector allows concurrent synthesis of curative adult and fetal hemoglobin, *Haematologica* (2021). DOI: 10.3324/haematol.2020.276634

Provided by Children's Hospital of Philadelphia