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Gene therapy breakthrough heralds treatment for beta-thalassemia

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Italian scientists pioneering a new gene transfer treatment for the blood disorder β-thalassemia have successfully completed preclinical trials, claiming they can correct the lack of beta-globin (ß-globin) in patients' blood cells which causes the disease. The research, published in *EMBO Molecular Medicine*, reveals how gene therapy may represent a safe alternative to current cures that are limited to a minority of patients.

The disorder β-thalassemia, also known as Cooley's anemia, is caused when a patient cannot produce enough of the ß-globin component of haemoglobin, the protein used by red blood cells to carry oxygen around the body. The lack of ß-globin causes life threatening anemia, leading to severe damage of the body's major organs. The condition is most commonly found in Mediterranean, Middle Eastern and Asian populations.

"Currently treatments are limited to lifelong regular blood transfusions, and iron chelation to prevent fatal iron overload. The alternative is bone marrow transplantation, an option open to less than 25% of patients," said Dr Giuliana Ferrari from the San Raffaele Telethon Institute for Gene Therapy in Milan. "Our research has focused on gene therapy: by transplanting genetically corrected stem cells we can restore haemoglobin production and overcome the disorder."

Diseases of the blood are good targets for gene therapy because it is possible to harvest stem cells from the patient's bone marrow. The team developed a tool to deliver the correct gene for ß-globin into these

harvested cells, a viral vector they called GLOBE.

The cells can then be genetically modified with GLOBE to restore hemoglobin production before being re-administered back into the patient via intravenous injections. The important focus of this work was not only to show that GLOBE can restore haemoglobin production in human cells, but that this genetic transfer-based approach does not impair the biological features of the cells and is not associated with any intrinsic risk for the human genome.

This research is not only crucial for developing a cure for one disease, but as Dr David Williams from the Harvard Medical School says, it may advance the entire discipline of gene therapy research

"This work represents the kind of translational studies that are required to move human investigations forward but are often difficult to fund and publish," said Williams. "Considering the inherent difficulties accompanying human research, studies like those reported in *EMBO Molecular Medicine* are extremely important for moving the field forward." As the Milan based team can now correct the defective production of beta-globin in patients' blood cells the next step will be to place the corrected cells back into the patient, a step which has already proven successful in mice.

Successful gene therapies are the results of very long studies and our research represents the most comprehensive pre-clinical analysis ever performed on cells derived from thalassemic patients" concluded Ferrari. "We believe this study paves the way forward for the clinical use of stem cells genetically corrected using the GLOBE vector."

More information: Roselli E.A., Mezzadra R., Frittoli M.C., Maruggi G., Biral E., Mavilio F., Mastropietro F., Amato A., Tonon G., Refaldi C., Cappellini M.D., Andreani M., Lucarelli G., Roncarolo M.G.,

Marktel S. and Ferrari G. “Correction of ß-thalassemia major by gene transfer in hematopoietic progenitors of pediatric patients.” EMBO Molecular Medicine, Wiley-Blackwell, July 2010. DOI: 10.1002/emmm.201000083