

# New gene therapy technique on iPS cells holds promise in treating immune system disease

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Researchers have developed an effective technique that uses gene therapy on stem cells to correct chronic granulomatous disease (CGD) in cell culture, which could eventually serve as a treatment for this rare, inherited immune disorder, according to a [study](#) published in [Blood](#), the Journal of the American Society of Hematology.

CGD prevents neutrophils, a type of white blood cell of the immune system, from making [hydrogen peroxide](#), an essential defense against life-threatening bacterial and fungal infections. Most cases of CGD are a result of a mutation on the [X chromosome](#), a type of CGD that is called "X-linked" (X-CGD).

While antibiotics can treat infections caused by X-CGD, they do not cure the disease itself. Patients with X-CGD can be cured with a hematopoietic stem cell (HSC) transplant from healthy bone marrow; however, finding a compatible donor is difficult. Even with a suitable donor, patients are at risk of developing graft-versus-host disease (GVHD), a serious and often deadly post-transplant complication that occurs when newly transplanted [donor cells](#) recognize a recipient's own cells as foreign and attack the patient's body.

Another treatment option under development for X-CGD is gene therapy, a technique for correcting defective genes responsible for disease development that involves manipulation of genetic material within an individual's blood-forming [stem cells](#) using genetically engineered viruses. However, this gene therapy has so far proved to be inefficient at correcting X-CGD. In addition, these engineered viruses insert new genetic material at random locations in the blood-forming stem cell genome, putting patients at significantly higher risk for developing genetic mutations that may eventually lead to serious blood disorders,

including [blood cancer](#).

In order to develop a more effective and safer gene therapy for X-CGD, researchers from the National Institute of Allergy and Infectious Disease (NIAID) at the National Institutes of Health (NIH) and The Johns Hopkins University School of Medicine embarked on a study using a more precise method for performing gene therapy that did not use viruses for the gene correction. Researchers removed adult stem cells from the bone marrow of a patient with X-CGD and genetically reprogrammed them to become induced pluripotent stem cells (iPS cells). Like embryonic stem cells, these patient-specific iPS cells can be grown and manipulated indefinitely in culture while retaining their capacity to differentiate into any cell type of the body, including HSCs.

"HSCs that are derived from gene corrected iPS cells are tissue-compatible with the patient and may create a way for the patient's own cells to be used in a transplant to cure the disease, removing the risk of GVHD or the need to find a compatible donor," said Harry L. Malech, MD, senior study author, Chief of the Laboratory of Host Defenses and Head of the Genetic Immunotherapy Section of NIAID at the NIH. "However, turning iPS cells into a large number of HSCs that are efficiently transplantable remains technically difficult; therefore, our study aimed at demonstrating that it is possible to differentiate gene corrected iPS cells into a large number of corrected neutrophils. These corrected neutrophils, grown in culture, are tissue-compatible with the patient and may be used to manage the life-threatening infections that are caused by the disease."

Typically, iPS cells from a patient with an inherited disorder do not express disease traits, despite the fact that the iPS cell genome contains the expected

mutation. The researchers were able to prove, in culture, that iPS cells from a patient with X-CGD could be differentiated into mature neutrophils that failed to produce hydrogen peroxide, thus expressing the disease trait. This is the first study in which the disease phenotype has been reproduced in neutrophils differentiated from X-CGD patient-specific iPS cells.

After discovering that the disease could be reproduced in cell culture, the researchers then sought to correct the disease and produce healthy neutrophils in culture. They used synthetic proteins called zinc finger nucleases (ZFNs) to target a corrective gene at a specifically defined location in the genome of the X-CGD iPS cells. The iPS cells were then carefully screened to identify those containing a single copy of the corrective gene properly inserted only at the safe site. The researchers observed that some of the gene-corrected iPS cells could differentiate into neutrophils that produced normal levels of hydrogen peroxide, effectively "correcting" the disease.

"This is the first study that uses ZFNs in specific targeting gene transfer to correct X-CGD," said Dr. Malech. "Demonstrating that this approach to gene therapy works with a single-gene disease such as X-CGD means that the results from our study offer not only a potential treatment for this disease, but more importantly, a technique by which other single-gene diseases can be corrected using specifically targeted [gene therapy](#) on iPS [cells](#)."

Provided by American Society of Hematology

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