Gene Therapy for Chronic Granulomatous Disorder

Chronic Granulomatous Disorder and Gene Therapy

Bone marrow transplantation (BMT) is a curative option for people with CGD with a tissue matched (HLA-matched donor), when conventional care and therapy fail. The major risk factors associated with BMT are graft-versus-host disease and inflammatory flare-ups at sites of infection. Nevertheless, the overall success rate of BMTs for those with an identically matched donor is 81% with an overall mortality of 15%. Gene replacement therapy for patients lacking a suitable stem cell donor is still in its infancy, but is already transitorily effective and has helped in several cases to overcome life-threatening infections.

Results

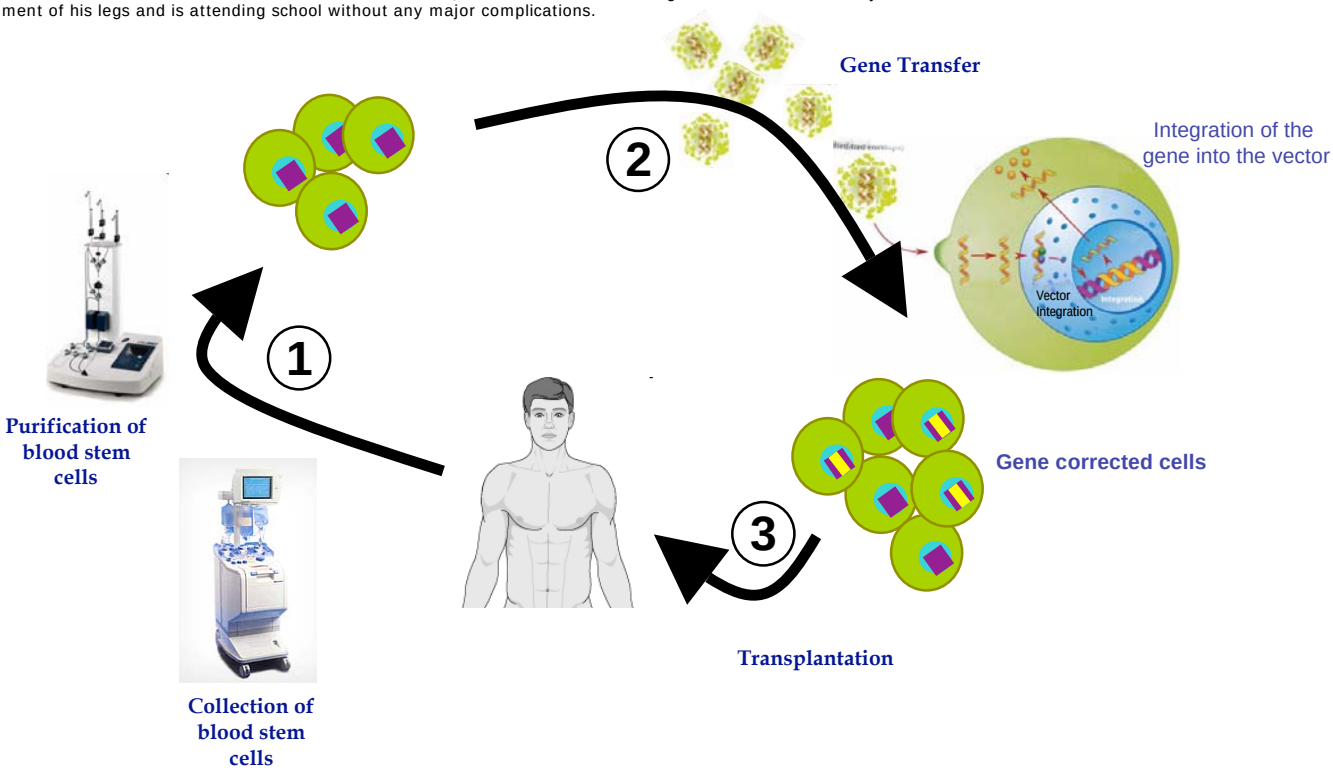
Since 2004 a total of 6 X-CGD patients have been treated by gene therapy (2 adults in Frankfurt, 1 child in Zurich and 2 adults and 1 child in London). In the two adults treated in Frankfurt gene marking and functional correction of phagocytes were high shortly after transplantation of gene modified cells, leading to the eradication of therapy resistant infections from which patients had suffered for many years. A third patient, a 5 years old child was treated in May 2005 in a similar way in Zurich. In this case only low levels of engraftment and gene correction were achieved. However the clinical benefit was clearly evident. Before therapy the patient was suffering from aspergillosis in the spinal cord leading to partial paralysis of his legs such that he could not walk. After GT treatment the patient has recovered movement of his legs and is attending school without any major complications.

How it works

Gene therapy is a technique for replacing a defective gene with a normal one. In simple terms it involves isolating a good gene from normal cells and then uses modified viruses as delivery vehicles (vectors) to transport the good gene into the patient's cells. Viruses had been designed through evolution, to serve as genetic material delivery systems. These properties have been adopted for gene therapy. However, for each type of viral based gene therapy vector, there are major disadvantages, which should be balanced with the therapeutic benefits. At present, retroviral vectors are the most commonly used gene delivery system.

The next generation of gene medicine

Current results indicate that in some cases the gene therapy may only last for a short time, and that the new gene can be 'switched off'. It is also known that the formulation of the genetic medicine can alter the way in which the cells behave, and in some cases this could cause them to grow uncontrollably, a bit like leukemia. To fix these problems, work is underway to make sure that the new genes cannot be switched off, but also cannot effect other innocent genes that may be close-by. This can be done through the remarkable technology of molecular biology which enables us to change genes and viruses that carry the genes in a favourable way.



Procedures:

① **Collection and purification of haematopoietic stem cells from the peripheral blood of CGD patients**

② **Incubation of the cells with the gene transfer vector (transduction)**

③ **Infusion of gene corrected cells into the patient**

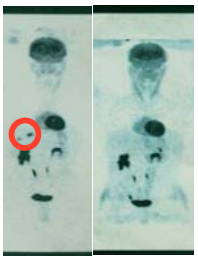
Addendum:

One of the adult patients died 27 months after treatment due to a severe sepsis with multiorgan failure. The available data indicate that the patient death was caused by a failure of gene modified cells to produce enough reactants to kill bacterial infections. Currently, new gene delivery systems are being developed to avoid this sad outcome in the future.

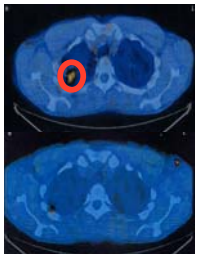
Clearing of infections after Gene Therapy

Gene therapy helps clear infections that are resistant to conventional treatment.

Before GT After GT



Clearing of a Staphylococcus aureus infection in the liver following gene therapy.



Before GT

After GT

Scan of a lung of a patient treated by gene therapy showing clearing of infection caused by Aspergillus.