Successes and setbacks of clinical gene therapy

The use of retroviral hematopoietic stem cell gene therapy to treat hereditary immunodeficiencies has achieved great success in resolving the actual symptoms of the disease, but many of the patients that underwent therapy developed leukemia later. Effective gene therapies involving gene shuttles that do not cause cancer are therefore required. The good news is that such therapies already exist.

The basic idea of gene therapy is amazingly simple: missing genetic information is transferred into the cells of a patient suffering from a life-threatening genetic defect in order to reconstitute the diseased cells’ ability to produce a vital protein from the transferred DNA.

Nature itself provides very efficient gene shuttles (also known as vectors) that are used to carry foreign genetic material into cells. Viral vectors are particularly effective gene shuttles. However, they have to be modified so that they do not cause adverse health effects, for example by blocking the virus’s ability to reproduce. Such methods have long been used in the production of vaccines.

However, gene therapy is a very complex medical treatment that is associated not only with great potential for treating monogenic diseases (i.e. diseases caused by modifications in a single gene occurring in all cells of the body), but which is also associated with significant risks. A child with a severe genetic defect became the first gene therapy patient more than twenty years ago. However, since then, gene therapy has had its ups and downs, has achieved unexpected successes as well as major setbacks. Some of the patients developed different diseases, while others died, showing that there are limits to the current use of gene therapy.

However, technological advances in recent years, especially with regard to the design of gene vectors and insights into how the transferred genes are integrated in patient cells and into their mode of action, have strengthened confidence in the improved safety of gene therapy trials as well as opening up the possibility of being able to treat previously incurable hereditary diseases.

The gene therapy of the Wiskott-Aldrich syndrome
Ten children who suffered from Wiskott-Aldrich syndrome (WAS), a rare genetic disease, were treated as part of a clinical gene therapy trial carried out in Germany between 2006 and 2009. Haematopoietic, i.e. blood forming stem cells were removed from the children’s bone marrow and the genetic defect was corrected by introducing a healthy copy of the WAS gene using a retroviral vector. The genetically modified cells were introduced back into the patients with the hope that they would produce normal protein and cure the patients. A team of researchers led by Dr. Anna Paruzynski, Dr. Manfred Schmidt and Prof. Christof von Kalle from the National Centre for Tumour Diseases (NCT) were instrumental in the first application of gene therapy for the treatment of WAS. The researchers from Heidelberg studied how the transferred gene sequences were integrated into the DNA of the haematopoietic stem cells.

Wiskott-Aldrich syndrome is a rare hereditary disease characterised by eczema on the entire body. © rarediseases.info.nih.gov

Wiskott-Aldrich syndrome is a rare, X-linked recessive monogenic disorder that affects the immune system. As the WAS gene is located on the X chromosome, the disease almost always only affects boys. WAS is characterised by the children’s high susceptibility to infections, bleeding and skin rashes. Left untreated, the disease leads to the early death of the children. Apart from gene therapy, the only chance of cure lies in the transplantation of blood stem cells collected from genetically matching donors. Stem cell transplantation was not possible for the children who were part of the WAS trial.

The health of the children improved significantly and quickly following gene therapy. “None of us, neither children, their parents or us doctors expected this to happen,” says Dr. Christian Braun, lead author of the latest publication reporting on the WAS trial. “We could show in the laboratory that the blood cells had been repaired and were functioning perfectly.” However, one to three years following gene therapy, seven of the ten children developed blood cancer (acute lymphocytic or acute lymphoid leukaemia). Although children with Wiskott-Aldrich syndrome have a greater chance of developing some types of cancer, “the rate of secondary malignancies was nevertheless unacceptably high,” the authors observed. The children with leukaemia had to undergo additional treatment. They received unrelated donor transplants, which led to complications and the death of two of the children. The remaining eight children are doing well.

However, the outcome of the WAS gene therapy trial suggests that a different form of gene therapy needs to be found in order to treat WAS effectively. Prof. Christoph Klein, principal investigator of
The clinical trial, comments: “The scientists must now try to optimise the method so that it becomes more effective and has a considerably lower risk for the patients.”

Retroviral gene transfer leads to leukaemia

Paruzynski, Schmidt and von Kalle then went on to study the molecular mechanisms that led to the development of leukaemia in the young WAS patients. The scientists analysed the mechanisms on the DNA level with unprecedented thoroughness as the authors, who are well-known international experts in the field of gene therapy trial safety, highlight in the publication. Their analyses showed that in successfully transformed cells, the integration sites of the retroviral genes were not randomly distributed across the genome, but that among the 25 most frequently affected genes 17 had already been known to be proto-oncogenes. They assumed that the proto-oncogenes had been activated in numerous cells by retroviral gene sequences, something that led to the uncontrolled proliferation of cells. The scientists from Heidelberg assume that the traditional retroviral vectors used in the trial were the causal factor of leukaemia development and highlight: “Further studies will be needed to determine the role of the genetic changes caused by retroviral gene transfer and of the underlying hereditary disease (i.e. WAS) in the development of leukaemia. It is absolutely certain that these disease cases help us understand how leukaemia develops.”

Looking for safe gene shuttles

It is also certain that the successful application of gene therapy depends on the use of transport vehicles with a superior safety profile. As an alternative to retroviruses, Italian researchers have used inactive lentiviruses as gene shuttles. These lentiviruses were made from the non-infectious components of HIV. The Italian researchers carried out two pilot studies, one with three boys suffering from a severe form of WAS, and the second with three patients who lacked the enzyme arylsulfatase A. The therapies were able to halt progression of the disease and alleviate the symptoms. None of the patients has to date developed leukaemia. However, the time since gene therapy was carried out is still too short and the number of patients too low for a conclusive judgement to be made.

The research group Molecular and Gene Therapy at the NCT led by Dr. Manfred Schmidt is involved in most international gene therapy trials focused on the treatment of genetic immune diseases. As part of the trials, the group monitors the composition and growth of blood forming cells with regard to the patients’ risk of developing some form of blood cancer. The research group has also shown that a genetically modified adeno-associated virus (AAV) used for the treatment of a very rare hereditary metabolic disease (lipoprotein lipases deficiency, LPLD) is not associated with the risk of developing cancer. The safety tests carried out by the researchers from Heidelberg were a prerequisite for the EMA’s (European Medicines Agency) approval of AAV as first gene therapy drug in the Western World (see BIOPRO article entitled “Europe’s first gene therapy”; link on the right-hand side). Manfred Schmidt hopes that if this vector proves suitable for LPLD gene therapy, it will also serve as a prototype for applying gene therapy to the treatment of other genetic diseases.

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Retrovirus model. © DKFZ

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