Hannover Medical School

Press Release

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Effective Gene Therapy for Children with Wiskott-Aldrich-Syndrome, a Severe Inborn Immunodeficiency Disease

In a first application of gene therapy for the treatment of Wiskott-Aldrich Syndrome, blood forming bone marrow cells have been corrected by gene transfer in Hannover, Germany. A team led by Professor Christoph Klein has succeeded in correcting symptoms of this rare, inherited immunodeficiency in 9 out of 10 children in a clinical trial. One patient did not receive a sufficient number of cells, and one patient unfortunately developed an acute T cell leukemia related to the treatment. In an article published in the New England Journal of Medicine this week, Klein and colleagues report on details of their trial's two first patients with four years of follow-up. "We are delighted about the possibility to offer a new form of therapy to this group of patients" says Klein. "However, we have to proceed very carefully, because the inherent risks of the retrovirus vector technology can produce serious side effects, as occurred in one of our patients." Earlier this year, Professor Klein received the renowned Leibniz Award of the German Research Foundation (DFG) for his work in pediatric immunology.

The Wiskott-Aldrich Syndrome

The first symptoms of Wiskott-Aldrich syndrome (WAS) occur in early childhood and include repeated serious infections, pneumonia, bleeding and rashes. WAS patients frequently develop autoimmune diseases, leukemia or lymphoma, and die of infectious complications when left untreated. Allogeneic blood stem cell (bone marrow) transplantation has been the only therapeutic option thus far. However, this approach requires a genetically matched donor and therefore, has not been available for all patients, and can produce serious side immunological side effects. "Immune complications of allogeneic stem cell transplantation can be quite severe in WAS patients" notes Dr. Kaan Boztug, a researcher in Christoph Klein's team and first author of the New England Journal of Medicine article. The disease is caused by a genetic mutation disturbing the formation of the Wiskott-Aldrich Syndrome protein (WASP). The protein is important for a functional cytoskeleton, which is required for maturation and activation of white blood cells forming the immune system and platelets required for blood clotting. The researchers could demonstrate by several tests that gene transfer can restore cytoskeletal function.

Treatment by transfer of a normal gene

The Wiskott-Aldrich Syndrome (WAS) gene is located on the X chromosome, and therefore the disease is exclusively found in boys, such as the five-year old Felix Ott. Shortly after being born in 2005, he had to be admitted to the intensive care unit because of severe bleeding. The diagnosis Wiskott-Aldrich Syndrome was

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made later, at age three. At this point, Felix's pediatrician anticipated a bad prognosis. In 2009, Felix received stem cell gene therapy. The researchers purified hematopoietic stem cells and corrected the genetic defect by introducing a healthy copy of the WAS gene using a retroviral vector. The genetically modified cells were reinfused and started to produce normal blood cells. Within a year after gene therapy, Felix´s corrected bone marrow generated functional platelets and white blood cells. The symptoms caused by dysfunctional blood cells completely resolved. He now enjoys a normal life and his father Oliver is quite joyful: "Today, Felix can play with other children and we don't have to handle him with kid gloves any more".

Possibilities and risks of gene therapy

For gene therapy, missing genetic information is transferred into body cells to reconstitute the diseased cells' ability to produce a vital protein from the transferred code. Nature itself provides very efficient gene ferries in the form of viruses. For gene therapy, the genetic information for making viral proteins is removed, and replaced by the healthy WAS gene. Ideally, a single application is sufficient for replacing gene function, and might avoid the necessity for lifelong medication.

Even though gene therapy is a simple concept, in clinical reality it requires a complex medical treatment and is associated not only with great potential but also with significant risks. Patient safety is a top priority in the pursuit of possibilities to cure rare diseases. Unwanted side effects of gene vector integration into the genome of cells include the activation of cellular genes involved in initiating cancer. Tight monitoring of bone marrow function for side effects is of great importance for the successful conduct of gene therapy trials. Prof. Christof von Kalle at the National Center for Tumor Diseases (NCT) in Heidelberg, Germany is an internationally renowned expert in gene therapy vector monitoring. His team regularly studies the treated WAS patients' cells for activation of cancer associated genes. "While we did not discover very large imbalances of cell growth in the first patients, this does not yet exclude more serious side effects developing later." First studies in cells from the leukemic patient seem to indicate that the therapeutic vectors have caused the initial stages of this severe side effect, which also occurred in previous gene therapy trials in Paris and London.

"New gene vectors can potentially prevent such side effects, but have not been available in a clinically usable format," says Klein. "We do hope that this technology will be available one year from now for the next generation of this trial."

Prior to clinical application of this gene therapy Klein's interdisciplinary team has closely worked with philosophers and bioethicists. "For our WAS children without suitable transplant donors, gene therapy offers a chance to return to a normal life, as Felix's example shows," explains Klein.

Care for Rare Foundation

Professor Christoph Klein and colleagues have established the Care-for-Rare-Foundation aiming to help children with rare diseases by promoting translational scientific studies and by enabling rapid access to state-of-the-art genetic diagnosis and innovative therapies. The Care-for-Rare Foundation collaborates with an international network of physicians and scientists and has a current focus on rare diseases of the immune system (www.care-for-rare.org).

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