

## Presse release

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### **Severe Combined Immuno-Deficiency The clinical trial put on hold**

In 2000, results from a clinical trial describing, for the first time, treatment of a disease by gene therapy were published in Science. The treatment was aimed at correcting the X-linked severe combined Immuno-deficiency (X-SCID), an inherited genetic disease. Since then, the first results have been confirmed by the success of the treatment in eight patients. This clinical trial is conducted at Hôpital Necker-Enfants Malades, in Paris, by Professors Marina Cavazzana-Calvo and Alain Fischer. The clinical trial was set up after a 6-year research project conducted at INSERM, with grants and funds from the Association Française des Myopathies (AFM).

In one of the patients enrolled in the clinical trial, a complication has recently been observed consisting in an uncontrolled lympho-proliferation which had to be treated. Investigations have been initiated to understand the cause of this event. As soon as the complication was detected, the other patients enrolled in the study and their families, as well as the scientific community have been duly informed. The other children treated are keeping well.

As a precautionary measure, and until analysis and identification of the mechanism(s) responsible, the clinical trial has been put on hold by the sponsor, in agreement with the French Medicine Agency (Afssaps).

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### **Severe Combined Immunodeficiency (X-linked)**

X-linked severe combined immunodeficiency (SCID-X) is a rare genetic disorder leading to a profound deficiency of host defenses against infections. It is caused by a block in the development of a subset of white cells, the T lymphocytes. The molecular mechanism responsible for the disease is known. It consists of a defective expression (or function) of a protein called  $\gamma_c$ , which is normally present at the cell membrane of lymphocytes precursors. In its absence, differentiation of T lymphocytes (and NK lymphocytes) cannot occur. The  $\gamma_c$  protein is part of a receptor receiving external signals required for cell differentiation.

Without treatment, the SCID-X1 condition leads to death during the first year of life. Since more than 30 years, it has been possible to treat successfully this disease by an allogeneic bone marrow transplantation from a HLA identical sibling. Unfortunately, no more than 20% of patients have such a donor. The other patients can be treated by a bone marrow transplantation from a partially incompatible donor (usually a parent). This therapy however carries a number of limitations: a mortality risk in the range of 20 to 30%; there is usually an incomplete development of immune defenses, requiring in most cases additional therapy (immunoglobulins) while, a decline in immune functions is observed after several years in some patients.

This is why research efforts have been undertaken to develop an alternative therapy, i.e. gene therapy.

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### Gene therapy of SCID-X1

It consists of inserting, in the genome of the bone marrow cells of the patients (those cells which are precursors of blood cells, among which lymphocytes) a normal copy of the  $\gamma c$  gene. Gene transfer is performed ex vivo. After bone marrow cells harvesting, these cells are admixed with a virus that contains the  $\gamma c$  gene. The virus is able to bind to marrow cells, penetrate the cells and induce gene integration into cell genome. It is a retrovirus derived from viruses able to infect murine bone marrow cells. The virus has been modified in a way that it cannot replicate (give rise to other viral particles) in the patient. A 6-year research program (1993 to 1999) has been undertaken at INSERM Unit 429 "Développement normal et pathologique du système immunitaire" at Necker Hospital in Paris in order to design the procedure, then ascertain its feasibility and potential toxicity. Experiments carried out in vitro and in a murine model of the disease demonstrated that the procedure was efficient in terms of gene transfer, whereas no toxicity was observed. Therefore, a clinical trial was proposed. Before being initiated, the clinical trial protocol obtained all necessary regulatory authorizations. The sponsor of the trial is Assistance Publique/Hôpitaux de Paris. The trial was initiated in March 1999 at Necker-Enfants Malades Hospital where all necessary facilities and expertise are present.

From March 1999 up to 2002, ten patients were treated, among whom 9 were infants with a complete deficiency in T lymphocytes. Results of this trial have been published in Science Magazine (2000) and the New England Journal of Medicine (2002). In brief, in 8 infants, a correction of immunodeficiency has been observed enabling these children to live normally. The ability of patients T lymphocyte precursor cells to divide once corrected by  $\gamma c$  gene transfer, accounts for the efficacy of this therapy.

In one patient, the treatment failed because corrected cells, after re-infusion were trapped in his abnormally enlarged spleen. This patient has received a rescue allogenic bone marrow transplantation which has partially corrected his immunodeficiency.

No adverse effect has been observed in these patients up to this year. They are all under regular scrutiny by visit to an outpatient clinic in order to assess the persistence of their immunodeficiency correction.

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### **An adverse effect in one of the treated patients with SCID-X1**

Recently, a complication of this gene therapy protocol has occurred in a patient, who was treated in October 1999. He is the fourth treated patient. Gene therapy led to the development of an efficient immune system, but, in spring 2002, an excess of a particular subset of T lymphocytes was noticed in patient's blood, during a regular check-up.

The lymphocytes count rose to high value at the end of the month of August associated at that time with clinical manifestations. The child, remained however in a good general status. Investigations have shown that the lymphocytes were monoclonal and that the virus integration site (the place where the genetic material of the viral vector is inserted in the genome) led to the deregulation of a given gene. Aberrant expression of this gene is likely responsible for the cell clonal proliferation. This event, called insertional mutagenesis is a known risk of (retroviral vector-mediated) gene therapy. However, all experimental and clinical data so far concurred to consider it as a very low risk event, limited to this form of gene therapy. Patient's cell proliferation is being presently treated.

Numerous additional investigations have been undertaken in order to elucidate the precise mechanism responsible for this cell proliferation. It is conceivable that additional factors can be involved (such as role of a viral infection, immunological stimulation and family predisposition). After completion of these investigations and assessment of the patient's response to the antiproliferative therapy, it will be possible to assess the exact significance of the side effect. This information will then be taken into account in proposing new strategies for gene therapy aimed at targeting bone marrow cells using retroviral vectors.

Meanwhile, by precaution, the clinical trial has been put on hold. Concerned families have been fully informed and the scientific community as well.