European Society of Gene Therapy (ESGT)
Press release

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- **Reports of a second serious adverse event in a clinical trial of gene therapy for X-linked severe combined immune deficiency (X-SCID)**

- **Position of the European Society of Gene Therapy (ESGT)**

News of a second, serious adverse event in a clinical trial of gene therapy for inherited, X chromosome-linked Severe Combined Immunodeficiency (X-SCID) were made public on January 14th. The US Food and Drug Administration, the Office for Biotechnology Activities at the National Institutes of Health, and the American Society for Gene Therapy have taken the unilateral decision to publicly release the information they had received on December 20th, 2002 from the group of French scientists performing the trial, led by Alain Fischer and Marina Cavazzana-Calvo at the Hôpital Necker Enfants Malade in Paris. The investigators had informed their scientific colleagues that the fifth of the eleven patients who received transduced stem cells developed a T-cell leukemia, and was receiving chemotherapy. The FDA has placed a temporary halt on gene therapy trials using retroviral vectors in blood stem cells. Following the US disclosure, the French Medicinal Product Safety Agency has issued a press release reporting the second case on January 15th. (http://afssaps.sante.fr/htm/10/filcoprs/030101en.htm).

This is the second serious adverse event to be reported in this trial. The first one was reported on October 2nd, 2002, when the French group issued a press release indicating that the fourth patient under treatment had developed a monoclonal lymphoproliferative disease (a leukemia-like disorder). The French investigators decided to share their data on this first adverse event with the scientific community at the ESGT annual meeting held in Antibes (France), on October 13th–16th, 2002. A transcript of the presentation, and the discussion that followed, is available on the ESGT web page at http://www.esgt.org. ESGT fully supported the investigators' and French regulatory authority's decision to put the trial on hold pending further investigations (see the ESGT positions posted on October 8th and 25th on the ESGT web site at http://www.esgt.org).

The French X-SCID gene therapy trial

Inherited X-SCID is characterized by an absence of both B and T cells of the immune system, leading to severe and recurrent infections that are usually fatal in the first years of life. Bone marrow transplantation (BMT) can be a successful treatment option, but it works bests when there is a fully compatible donor. Unfortunately, this is the case for less than one third of X-SCID children. For the others, unmatched BMT carries a high risk of graft failure, graft-versus-host disease, lymphoma, and other medical problems.

The gene therapy trial carried out by Fischer and co-workers involves integration of a therapeutic gene into the X-SCID patients' own bone marrow cells. This approach avoids rejection problems and the

need of a compatible donor. Dr. Cavazzana-Calvo reported that gene therapy has achieved effective and life-saving immune reconstitution in 10 out of 11 patients treated so far. All patients are alive, and have been able to lead a normal life for periods up to 3 years. From a clinical point of view, these patients should be considered cured by this pioneering gene therapy treatment.

One of the patients (the fourth) developed a monoclonal gamma-delta T-cell lymphoproliferative disorder30 months after treatment. The investigators promptly recognized early signs of the disease, followed its progression, and eventually decided to start a chemotherapy. The patient responded to the therapy, and is currently followed by the team. The causes of this adverse events have not been conclusively established so far. The investigators reported that the retroviral vector used to transfer the therapeutic gene into the patient's hematopoietic cells was found, in the malignant cells, inserted in a gene - called LMO2 - known to cause T-cell leukemia if activated inappropriately, for instance as a consequence of a chromosomal translocation. The investigators speculated that the insertion of the retroviral vector might have caused an abnormal expression of LMO2, which in turn might have triggered the leukemic transformation. Other factors could have potentially contributed to the malignant transformation, including malfunction of the therapeutic gene, which encodes a common subunit of various T-cell growth factor receptors. In her presentation to the ESGT annual meeting, Dr. Cavazzana-Calvo mentioned a history of childhood tumors in the patient's family, and reported an episode of chickenpox infection in this patient preceding the occurrence of the malignancy, which might have caused an abnormal proliferative expansion of immunoreactive T-cells. She also reported that the leukemic cells harbored at least a portion of the chickenpox (varicella-zoster) herpes-like virus (as assessed by a molecular test), and that the leukemic cells carried an additional molecular abnormality, a translocation between chromosomes 6 and 13, which does not involve the LMO2 gene.

The second adverse event involves a 3-yr old patient who was treated at the age of 3 months for X-SCID following a gene therapy protocol almost identical to that of the first patient who developed a leukemic disorder (patient 4). In the month of December 2002, an uncontrolled, alpha/beta T-cell proliferation was found in this patient. Similar to the first adverse event, the retroviral vector was found integrated in the proximity of the LMO-2 gene in the proliferating T-cells. Unlike the first child, this subject did not experience intercurrent infections, and is not known to have a family history that would be predisposing to cancer. Both children were treated at a very early age (one to three months) and received high doses of genetically modified cells.

Pre-clinical studies of the gene therapy approach used in the X-SCID study had shown no evidence of leukemia or other forms of cancer, and no similar adverse events have been reported in many previous gene therapy trials involving the use of retroviral vectors, including those addressing another form of severe combined immunodeficiency (the ADA-deficient SCID), which were initiated in the U.S. and in Europe more than a decade ago.

The position of ESGT

Patient safety is the major consideration in early clinical studies, and all possible efforts must be made to minimize the risks for the patients involved. The occurrence of leukemic complications in two out of ten treated patients in less than a year is a clear sign that the gene therapy treatment for X-SCID, as it was originally designed, involves an unforeseen and unexpectedly high risk of causing cancer. The repeated involvement of the LMO-2 gene as a site of insertion in the proliferating T-cell clones strongly suggests that the abnormal expression of this gene constitutes a high risk in the context of this treatment for this particular disease. ESGT, as an association of professionals dedicated to the development of gene and cell therapies, encourages and fully supports the efforts of the French investigators and their collaborators to understand the causes of these adverse events. The French group has already performed extensive studies in a very short time period in order to provide the families, and scientific/medical community with an impressive amount of information concerning these patients. ESGT members are ready to work with European regulatory authorities to continue the thorough investigation of these adverse events, and to evaluate any implications they might have for other gene therapy trials using vectors and procedures similar to those used by the French group.

ESGT recognizes the need for more pre-clinical investigation in assessing the risk of gene therapy, including more basic research in the development of safer gene transfer vectors. At the same time,

ESGT recognizes that there is no real substitute for clinical investigation, and that a correct assessment of the risk/benefit ratio for every patient involved in a clinical trial is the first and most important ethical criterion. As the history of this trial demonstrates, risk assessment cannot be based entirely on the results of pre-clinical investigation.