SAN RAFFAELE TELETHON
INSTITUTE
FOR GENE THERAPY
(HSR-TIGET)

Milan, July 20, 2010

Dear colleague,

The present letter is to update you on our clinical experimentation of gene therapy for the treatment of Metachromatic Leukodystrophy (MLD), currently active in the San Raffaele Telethon Institute for Gene Therapy (HSR-TIGET), in Milan. The study was recently approved (on March 2010) by the Italian Regulatory Authorities and is currently open to patients' recruitment.

The clinical experimentation has as objective the evaluation of the effectiveness and the safety of the treatment in study (gene therapy based on hematopoietic stem cells and lentiviral vectors) in a cohort of 8 MLD patients.

The first patient, with a molecular familiar history compatible with a diagnosis of late infantile MLD, has been recently treated being in a pre-symptomatic stage of his disease. Thus far, we can report a favorable outcome of the transplant procedure with a good bone marrow recovery and the short-term safety of both the conditioning regimen and stem cell transduction with lentiviral vectors. Only the long-term follow up would allow assessing the efficacy of the treatment in preventing and/or attenuating disease associated symptoms.

In the hope to be able to offer a hope of benefit to the patients and their families, we confide in Your precious collaboration for the recruitment of the patients for this clinical trial and we remain to disposition for any explanation at the following addresses:

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Gene therapy

Gene therapy is based on the principle that every illness caused by an alteration of a known gene can be cured by inserting, through viral vectors, a functional copy of the gene in the sick cells of the patient. In the case of the MLD, it is problematic to insert the functional gene in the sick cells of the central and peripheral nervous system for the inaccessibility of these organs. It is, however, possible, by using appropriate gene transfer systems, to correct in a stable way hematopoietic cells that can transport then the functional enzyme to the affected nervous system. With the purpose to realize this, we have drawn a gene therapy strategy based on the transplantation of hematopoietic stem cells transduced with a lentiviral vector

containing the human normal Arylsulfatase A (ARSA) gene, able to generate by their differentiated progeny a permanent source of the functional enzyme for the affected tissues. Such strategy, for many aspects similar to the transplantation of hematopoietic cells from healthy donors, is set as a less risky and more effective alternative to allogeneic transplantation thanks to the use of autologous, patient's cells genetically corrected by means of lentiviral vectors (which allow an above-physiological expression of the enzyme in the hematopoietic cells).
The safety and the effectiveness of this approach have been shown in the preclinical model of the disease, in which we documented the prevention and the correction of the signs and symptoms of the pathology following the treatment. To the light of such results, we have therefore implemented a clinical protocol for the transfer of such therapeutic strategy to MLD patients.

The clinical protocol

This research is conducted within the Fondazione Centro San Raffaele del Monte Tabor in Milan, in the Pediatric Clinical Research Unit of HSR-TIGET and in the Pediatric Immunohematology and Bone Marrow Transplant Unit at HSR.
Study promoter is the Fondazione Centro San Raffaele del Monte Tabor, in the person of the HSR-TIGET Director Prof. Luigi Naldini. The main financial sponsor is the Italian Telethon Foundation.
The physicians responsible of the study are:
Dr. Alessandra Biffi (Principal Investigator; Project leader at HSR-TIGET & Staff Pediatrician in the Pediatric Immunohematology and Bone Marrow Transplant Unit at HSR);
Dr. Maria Sessa (Principal Investigator; Project Leader at HSR-TIGET & Staff Neurologist in the Nuerology Department at HSR)
Dr. Attilio Rovelli (Co-Principal Investigator; Director of the Bone Marrow Transplantation Center of the Pediatric Department, San Gerardo Hospital, Monza);
Prof. Luigi Naldini (Co-Principal Investigator; Director of HSR-TIGET)
Prof. Maria Grazia Roncarolo (Co-Principal Investigator and Director of the Pediatric Immunohematology and Bone Marrow Transplant Unit at HSR; HSR Scientific Director).

The study is single center, in open, not randomized, perspective, comparative with a non-contemporary population of controls from us studied within a clinical study of natural history of the disease. As expected from the criterions for experimentation in pediatric patients, the study is a Phase I / II, therefore facing the evaluation not only of the safety but also of the effectiveness of the treatment.
The recruitment of the patients is international. The costs of the study are entirely to load of the HSR-TIGET.
The study foresee the enrollment of patients in the pediatric age affected from MLD, diagnosed through dosing of ARSA enzymatic activity and/or genetic analysis, that fullfil the following characteristics:

- Late infantile MLD in pre-symptomatic phase (in presence of a case index in the family);
- Early juvenile MLD in pre-symptomatic (in presence of a case index in the family) phase or within the first 6 months from the onset of the symptoms.

The plan of treatment consists of four phases:

- Bone marrow explant of the patient with isolation of the stem cells to be submitted to gene transfer;
- Manipulation of the cells and gene transfer with the lentiviral vector;
- Patient's conditioning, based on the alkylating agent Busulfan;
- Re-infusion of the manipulated stem cells.

Besides the safety end points of the treatment (related to the conditioning regimen and to the use of the lentiviral vectors), we will evaluate as primary efficacy end points an improvement / stability in the motor performances assessed by the "Gross Motor Function Measure, GMFM" 24 months after the treatment, in comparison to the scores obtained in a cohort of untreated patients of peer age, and a significant increase of the ARSA activity in the patients' hematopoietic cells measured 24 months after the treatment, in comparison to the pre-treatment values.

The follow-up post-treatment will be performed in the three years following the gene therapy, and an additional follow-up is anticipated for the 5 following years at the end of the study, according to the Italian Regulation (D.M. 2 March 2004)).

The Institute

The HSR-TIGET (http://www.fondazionesanraffaele.it) was funded in 1995 as joint-venture among the Scientific Institute San Raffaele and the Telethon Foundation for the research and treatment of rare genetic diseases. Main goal of the Institute is to be a center of excellence in all the phases of the research from basic to clinical gene and cellular therapy, from the experimentation of new therapeutic strategies in the animal models of disease up to their clinical testing in the patients. Particularly remarkable effort is related to the development of protocols of gene therapy based on the use of hematopoietic stem cells. The therapeutic success from us obtained in the treatment of a serious form of congenital immunodeficiency (ADA-SCID) represents today the most convincing demonstration of the effectiveness and safety of such approach.

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