

joint press release

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**Hematopoietic stem cell treatment with a new gene therapy vector:
A first success treating a brain disease**

Two children with adrenoleukodystrophy (ALD), a fatal brain disease, have been successfully treated with a new gene therapy vector. Two years after treatment, the disease evolution has been stopped, and no adverse effect of the gene therapy has been observed so far. The results of this clinical trial conducted by Drs Nathalie Cartier and Patrick Aubourg (Inserm, France) in collaboration with European partners have just been published in Science magazine. This first human use of HIV-derived vectors (lentivirus) turns hopes scientists had in therapeutic application of gene therapy into reality.

An in-depth and innovative analysis of the genetic events occurring in the corrected cells has been conducted by the laboratory of Professor Christof von Kalle and Dr. Manfred Schmidt (National Center for Tumor Diseases and German Cancer Research Center, Heidelberg, Germany). As has been demonstrated in previous studies with retroviral vectors, this analysis is crucial for the safety and long-term success of the therapy. "Even if we still have to remain cautious, no deleterious effect due to the insertion of the vector in the genome has been detected" Christof von Kalle explains. "For the first time, we managed to have a high percentage of stem cells expressing the therapeutic gene", Nathalie Cartier continues. "This is also the first time that a serious brain disease has been successfully treated by gene therapy.

ALD is a rare genetic disease of the leukodystrophies family (hereditary diseases of the brain myelin). Its most serious and frequent form, affecting children as well as adults, leads to progressive myelin destruction and death. Until now the only available treatment was a bone marrow transplantation procedure developed by Professor Aubourg in the nineties. However, this treatment is limited by the lack of a compatible donor and is often associated with severe or even lethal complications, particularly for adults.

The new therapeutic approach tested in this phase I/II clinical trial is based on the transplantation of the own patient's hematopoietic stem cells corrected by gene therapy. It therefore eliminates the need for a donor and avoids the risk of graft rejection or graft versus host disease. Bone marrow stem cells (hematopoietic stem cells) are collected from the patient and corrected with a functional version of the deficient gene by means of a new gene therapy vector derived from a modified and inactivated form of the HIV virus. As for a normal transplantation, the corrected cells are re-injected to patients and some of them, by a physiological process, migrate into the brain, where they play their beneficial role.

This clinical trial is the outcome of more than 10 years of research performed by Dr Nathalie Cartier in Inserm labs, under the supervision of Pr. Patrick Aubourg. "All treated patients are

doing well: the progression of the disease stopped a few months after the auto-transplantation. None of the side effects reported in other gene therapy treatment have been detected so far, even with cutting-edge methods”, explains Nathalie Cartier, research director at Inserm.

A scientific success supported by a network of partners

This clinical trial was conducted in the Pediatric Endocrinology and Neurology department of Saint Vincent de Paul Hospital (AP-HP), led by Professor Pierre Bougnères. Inserm is the promoter of the clinical trial, and a follow-up of the trial was done by both AP-HP and the Inserm Public Health department. The extensive experience of bone marrow stem cells use and transplantation brought by Professors Marina Cavazzana-Calvo, Salima Hacein-Bey and Alain Fischer (Hôpital Necker – AP-HP) was also critical for the project.

The research was supported for many years by Inserm (with evaluation and clinical studies follow up), as well as by AP-HP for the clinical application (PHRC programs). Besides, the project has always been supported by ELA (European Leukodystrophy Association), the association of leukodystrophic patients and AFM (Association Française contre les Myopathies) and the STOP-ALD foundation in the US. ELA: “We have been supporting the work of Pr Patrick Aubourg’s team for many years; the success of this clinical trial strengthens the hope of families affected by leukodystrophies”

For Laurence Tiennot-Herment, president of AFM: “For more than 20 years, thanks to the Telethon fundraising, we constantly support the research leading to tomorrow’s medicine. After getting the first results in immune deficits gene therapy, we are convinced that this new success paves the way for a decade of positive outcomes for other diseases. Biomedical revolution is on its way. Here is the proof that, all together, we can be stronger than the disease.”

The development of such large projects involves many actors, particularly for the clinical trial achievement. For each step, from the vector production to the toxicology and clinical studies, a complex network of public/private partnership has been put together. The existence of such a network requires an exquisite control of intellectual property, research collaborations and licence agreements. Inserm Transfert, Inserm Technology Transfer private subsidiary, has been coordinating this network for 3 years now.

The next steps for Drs Nathalie Cartier and Patrick Aubourg are to extend the clinical trial in France by recruiting new patients, including adults. The two researchers also plan on launching a similar trial in the US. These very positive results obtained in ALD pave the way for the development of similar treatments targeting other diseases using lentiviral vectors.

A picture is available at:

http://www.dkfz.de/de/presse/pressemitteilungen/2009/images/vonKalle_Science_Proteinexpression.jpg

Legend: Patient’s CD34+ progenitor cells express the therapeutic gene more than 2 years after the treatment (red: expression of the ALD protein, blue: cell nucleus)

Credit: Patrick Aubourg, INSERM U745

The German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) is the largest biomedical research institute in Germany and is a member of the Helmholtz Association of National Research Centers. More than 2,000 staff members, including 850 scientists, are investigating the mechanisms of cancer and are working to identify cancer risk factors. They provide the foundations for developing novel approaches in the prevention, diagnosis, and treatment of cancer. In addition, the staff of the Cancer Information Service (KID) offers information about the widespread disease of cancer for patients, their families, and the general public. The Center

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Contact:

Dr. Stefanie Seltmann
Presse- und Öffentlichkeitsarbeit
Deutsches Krebsforschungszentrum
Im Neuenheimer Feld 280
D-69120 Heidelberg
T: +49 6221 42 2854
F: +49 6221 42 2968