



Evry/Paris, 16 October 2008

PRESS RELEASE

Huntington's disease First graft of human embryonic stem cells successful in the animal

A team of researchers led by Anselme Perrier of the Institute of Stem Cells for the Treatment and Study of Monogenic Diseases (Inserm/UEVE UMR861, I-STEM, AFM joint research unit) directed by Marc Peschanski, has just succeeded in performing a first graft of human embryonic stem cells in an animal model for Huntington's disease. The researchers have thus developed a protocol for transforming these cells into the type of neuron specifically affected in Huntington's disease. Following this, they demonstrated that neural progenitors from embryonic stem cells could differentiate themselves into neurons in rat brains presenting lesions similar to those observed in humans.

This work is available online on the PNAS review website. It was in part financed by the AFM (French Muscular Dystrophy Association) thanks to Téléthon donations.

Huntington's disease is a genetic disease which causes the progressive degeneration of one region of the brain – the striatum. The anomaly at the origin of the disease affects the gene named IT15 situated on chromosome 4 and causes the repetition a great many times of the CAG triplet, a DNA sequence. This leads to the deterioration of the gene product, huntingtine. This mutated protein becomes toxic for the neurons producing it by forming aggregates in their nuclei, causing their dysfunction.

The prevalence of Huntington's disease is around 3 per 10 000 in Western European populations. Transmitted by autosomal dominant mode, it seems **the most frequent monogenic disease** affecting the brain. Early symptoms of the disease generally appear in adult patients between 35-40 years old, and include minor motor and cognitive disorders. These early symptoms rapidly give way to more serious symptoms such as involuntary movements (chorea), a decline of cognitive capacity and personality problems. Due to the rapid progression of the motor, psychiatric and cognitive symptoms, the patients are in constant need of help and medical care.

While there exist several drugs capable of limiting the motor and behavioural disorders linked to Huntington's disease, there is **at present no means of stopping or reversing its progression**. Most Huntington's disease patients die within a period of 15-18 years following the appearance of the first symptoms.

Huntington's disease constitutes a prime target for a cell therapy approach since the brain lesions are located specifically in the striatum. This therapeutic strategy has already demonstrated its effectiveness during a clinical trial during which long-term clinical improvements were observed following human foetal neuroblast grafts (European multicentred clinical trial under way, coordinated by Prof Anne-Catherine Bachoud-Lévi).

However, the technical difficulty in obtaining foetal grafts makes it necessary to look into alternative cell sources.

This is why Anselme Perrier's team became interested in the therapeutic potential of human embryonic stem cells (hES). To begin with they developed a protocol enabling the differentiation of hES into progenitors and striatal neurons. Once the protocol had been established, they carried out the graft of striatal cells from hES in the rat, the experimental model for Huntington's disease. In this way they obtained grafts containing a large number of striatal neurons.

This work forms the first successful stage in finally developing a treatment for Huntington's disease in humans using human embryonic stem cells. The researchers are continuing to study the profile and characteristics of the neurons obtained following the graft. The next step is to study the therapeutic potential of these embryonic stem cells as well as the risks of overproliferation or tumorigenesis linked to this kind of graft in the monkey. In particular, the cognitive and behavioural effects of this kind of graft will also be observed.

Created on 1 January 2005, I-Stem is a centre of research and development dedicated to the study of the therapeutic potential of human embryonic stem cells and its application to rare genetic diseases. The AFM, Inserm and the University of Evry-Val-d'Essonne are all founder members. I-Stem distinguished itself in 2007 by publishing results that demonstrated for the first time that human embryonic stem cells could differentiate themselves into cardiac cells in the failing hearts of rats (this work was the result of collaboration between research teams led by Michel Puc at (Inserm/UEVE UMR 861, I-STEM, AFM) and Philippe M enasch e (Inserm Unit 633)).

For further information:

Striatal progenitors derived from human ES cells mature into DARPP32 neurons in vitro and in quinolinic acid-lesioned rats. *Laetitia Aubry, Aurore Bugi, Nathalie Lefort, France Rousseau, Marc Peschanski and Anselme L. Perrier. PNAS (on line).*

Press contacts:

AFM : Mathilde Maufras, Delphine Carvalho - t el. : 01 69 47 29 01, presse@afm.genethon.fr

Inserm : Priscille Rivier e - t el. : 01 44 23 60 97, presse@inserm.fr

University of Evry : Maryvonne de La Taille - t el. : 01 69 47 70 64, maryvonne.delataille@univ-evry.fr