Parkinson's disease: an immense step forward thanks to gene therapy

A French and English team (AP-HP, Inserm, UPEC, CEA/Mircen, Oxford Biomedica, Cambridge University) has conducted a clinical phase 1/2 gene therapy study among patients suffering from an evolved form of Parkinson's disease.

Fifteen patients were able to benefit from this new treatment, which involves injecting a vector expressing the genes of three enzymes that are essential for the biosynthesis of dopamine, which is lacking in Parkinson's disease. Thanks to this therapy certain cells in the brain begin to produce and secrete dopamine again. In all the patients, the motor symptoms of the disease were improved for up to 12 months after administration of the treatment.

After a period of four years, this study is at this stage demonstrating innocuousness and tolerance of the lentiviral vector used for the first time in human beings.

This study was coordinated by Prof. Stéphane Palfi, head of neurosurgery at Henri-Mondor Hospital (AP-HP) within the framework of the neurolocomotor research cluster directed by Prof. Césaro.

It is the subject of a publication in The Lancet, embargoed until 10 January 2014 - 00h01 GMT/01h01 French time*.

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Parkinson's: a common neurodegenerative disease

With about 120,000 patients in France, Parkinson's disease is the most common neurodegenerative disorder after Alzheimer's disease. It essentially manifests itself through motor symptoms that steadily grow and become more severe such as trembling, rigidity of the limbs and diminished movement of the body. This pathology is due to the degeneration of neurons that produce dopamine, a neurotransmitter that participates in motor control.

Currently, the treatment of people affected by this disease consists of taking medication that mimics the action of the dopamine missing in the brains of these patients. While this treatment makes it possible to improve motor activity considerably during the first stages of the disease, severe undesirable effects appear at the end of this time such as fluctuations in the effect of the treatment and abnormal involuntary movements, called dyskinaesia.

Developing a new treatment that permits the physiological restoral of missing dopamine

For several years, experts on Parkinson's disease, researchers and doctors, have held the hypothesis that the intermittent intake of medication during the day alters the functioning of the brain by stimulating neurons in an excessively irregular manner. This phenomenon would constitute the origin of the complications connected with dopaminergic treatment.

The currently most pressing issues in the treatment of Parkinson's disease thus concern the development of a technology that would make it possible to induce:

- sustained dopaminergic stimulation;
- local dopaminergic stimulation in order to induce beneficial motor effects while avoiding the complications that follow stimulation in other regions of the brain not affected by Parkinson's disease .

This is why researchers today are turning to gene therapy, which consists of causing a therapeutic gene to be expressed directly by brain cells.

Gene therapy consists of introducing therapeutic genes in vivo so that they express directly in the targeted cells.
It rests on the use of viral vectors such as lentiviruses, adenoviruses and AAVs (adeno-associated viruses), which have the ability to introduce their genetic material into the nucleus of host cells.
Some requirements must be absolutely satisfied for a wild virus to be able to be transformed into a vector with the ability to ensure the transfer of genes of therapeutic interest in complete security. These viral envelopes are stripped of their properties for multiplication and rendered non-pathogenic.

The work of Prof. Palfi: Increasing the synthesis of dopamine through gene therapy

In the majority of cases, Parkinson's disease does not have a genetic origin. However, the biochemical modifications responsible for the symptoms can be corrected by using a gene therapy strategy of the 'replacement or restoral of function' type in order to increase the synthesis of dopamine (by expressing genes involved in the biosynthesis of dopamine) and restore the function of dopaminergic cells partially.

It is this approach that was adopted in the phase I/II biomedical study coordinated by Prof. Stéphane Palfi (Henri-Mondor Hospital, AP-HP), the results of which have just been published.

Fifteen patients were operated on by Prof. Palfi, coordinating investigator, in two centres of excellence in neurosurgery – Henri Mondor Hospital (AP-HP) in France and Addenbrookes Hospital in Cambridge, UK.

For the first time in human beings, the team used a lentiviral vector which expresses the genes of three enzymes – AADC (decarboxylase of aromatic amino acids), TH (tyrosine hydroxylase) and CH1 (GTP-cyclohydrolase 1) – essential in the biosynthesis of dopamine. The product was administered in the area of the brain called the striatum during a heavy surgical operation.

Once in the right place, the genes contained in the lentivirus can express themselves and reprogramme cells, which begin to produce and secrete dopamine in the extracellular environment.

Three increasing dosage levels (1×, 2× and 5×) were tested.

***'This biomedical gene therapy study shows innocuousness over the long-term transfer of genes by the lentiviral vector when it is injected directly into the brain of patients suffering from Parkinson's disease', explains* Prof. Stéphane Palfi**. *'The clinical analysis suggests that the vector used enables a reduction in motor symptoms depending on the vector dose administered, with the strongest dose being the most effective* .**

The objective of future clinical developments of the vector will be to confirm an improved viral construction that would make it possible to induce an increased release of dopamine (phase 2a). This phase will be followed by a study of the therapeutic effect of ProSavin® by comparing a group of patients receiving the treatment and another group not receiving the treatment (phase 2b). This study, which is pioneering the use in gene therapy of a lentivirus injected in situ, will definitely open up new therapeutic perspectives for diseases of the nervous system.'

Architecture of phase I/II clinical trial

The local and sustained production of dopamine in vivo was restored in 15 patients suffering from an evolved form of this disease. The long-term monitoring of these patients (4 years) evidenced undeniable innocuousness, tolerance and signs of the therapeutic effectiveness of the viral vector depending on the administered dose, with the strongest dose of the vector inducing the most substantial therapeutic effects.

Partners

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1. ProSavin®, developed on the basis of equine infectious anaemia virus (EIAV).

Portfolio

Photos and rush videos available on demand from the press service of AP-HP.

Key figures

15 patients treated

1 lentiviral vector used for the first time in humans

3 dosage levels tested

Research initiated in 2009

This clinical trial follows on from a preclinical study published in 2009, which showed for the first time the effectiveness and innocuousness of the medication in an animal model. Carried out within the framework of the MIRCen translational platform of the CEA, it has opened the door to the clinical study of ProSavin®.

AP-HP, Assistance Publique – Hôpitaux de Paris, is the university hospital centre (UHC) of Île-de-France and the first UHC in Europe. Its 92,000 professionals are committed to offering high-quality care to all, 24 hours a day. The 7 million people cared for each year benefit from the most advanced treatment in all the areas of the medical disciplines.

The Henri-Mondor University Hospitalsoffer excellent recourse services in medicine and surgery, geriatric and specialised follow-up and rehabilitation care, sector and university psychiatry and a complete geriatric network for two health catchment areas. The Henri-Mondor University Hospitals are a referral centre in Île-de-France for the treatment of Parkinson's disease. Key figures: 90,000 hospitalisations and external consultations in 2012; 3,139 beds; 8,000 professionals.

Created in 1964, the Institut national de la santé et de la recherche médicale (Inserm) is a public establishment, under the double tutelage of the Ministry of Higher Education and Research and the Ministry of Health. Its researchers are dedicated to the study of all diseases, from the most common to the most rare. Inserm supports approximately 300 laboratories spread throughout France. All the teams together amount to approximately 13,000 researchers, engineers, technicians and managers. Inserm is a member of the National Alliance for the Life and Health Sciences, founded in April 2009. Inserm celebrated its 50th anniversary in 2014 .

With 30,000 students and 12 faculties and institutes, Université Paris-Est Créteil Val de Marne (UPEC) is the largest multi-disciplinary university, including health, in Ile-de-France. Created in 1971, UPEC is a successful collective venture that today offers a complete range of training programmes (from university degrees in technology to doctorates) and has 31 laboratories that cover almost all disciplines.

The CEA is active in four major areas of research, including health technologies. Over 1,000 researchers and technicians contribute to this sector, from fundamental research to biomedical applications in neurology, oncology, immunovirology, etc. The CEA's contribution to the clinical study of Parkinson's disease involved the following two biomedical platforms:
- MIRCen, a translational research infrastructure dedicated to biotherapies and imaging in the domain of neurodegenerative diseases .
- Le Service Hospitalier Frédéric Joliot, which is developing functional and molecular imaging, mainly with the help of positron emission tomography, for applications in neurology, oncology and psychiatry.
For more information, go to www.cea.fr.