



Press release

Gene therapy Encouraging results in a Phase I clinical trial in limb-girdle muscular dystrophy type 2C

Evry (France), January 12, 2012 - **The results of a Phase I clinical trial of gene therapy for limb-girdle muscular dystrophy type 2C (a rare neuromuscular disease) have just been published in the journal *Brain* on January 11, 2012.** The trial started in December 2006 and has been sponsored by Généthon (the not-for-profit research lab created by the French Muscular Dystrophy Association (AFM) and which is funded almost exclusively by donations from France's annual Telethon). The trial at Pitié-Salpêtrière (AP-HP) is being led by principal investigators Professor Serge Herson (Head of the Department of Internal Medicine 1) and Professor Olivier Benveniste (Institute of Myology). The study's primary objective was to evaluate the safety of local injection of increasing doses of an adeno-associated virus (AAV) vector harboring a "healthy" copy of the gene for gamma-sarcoglycan (the defective protein in this disease). Secondary objectives included the assessment of local and systemic immune reactions and the quality of gene transfer in the injected muscles in terms of efficacy, expression and distribution.

Nine non-ambulatory patients (aged from 16 to 38) were included in the trial between December 2006 and December 2009. Three increasing doses of an AAV1 vector bearing the normal gamma-sarcoglycan gene were injected into a forearm muscle. One month after the injection, a biopsy was taken from the treated zone and analyzed.

The trial's results have just been published and are encouraging. Above all, the injections were well tolerated and not associated with adverse physical or biological effects. Furthermore, assays in five patients revealed the presence of RNA produced from the therapeutic gene (RNA is the intermediate genetic material between the gene and the protein). Immunohistochemical analysis of injected-muscle biopsy specimens showed γ SGC expression in three out of the three patients who received the highest dose. Furthermore, in one of these patients (who had received the highest dose of treatment), a western blot assay revealed that normal protein gamma-sarcoglycan was being expressed in the muscle fibers. Thanks to gene therapy, the missing gamma-sarcoglycan protein was being produced anew. Professor Serge Herson commented that *"the results of this trial exceed our expectations. In addition to confirming the treatment's lack of toxicity (the study's primary objective), we were able to make progress in other areas, such as trial logistics, immunological aspects and even the optimal*

dose for treating a set of muscles efficaciously. This result is especially interesting because it means that we have established the dose threshold above which the treatment becomes efficacious. That's very rare in a Phase I trial".

The physicians and researchers at Généthon, the Institute of Myology and Pitié-Salpêtrière (AP-HP) are continuing their work. They intend to set up a new trial in which an AAV8 vector will be used to treat a whole limb.

Limb-girdle muscular dystrophy type 2C (LGMD2C) is due to a lack of gamma-sarcoglycan protein. In muscle cells, the sarcoglycans form a complex that contributes to the stability and mechanical resistance of the cell membrane during muscle contraction. The lack of a single type of sarcoglycan often leads to disappearance of the whole complex. The membrane becomes more fragile as a result, leading to degeneration of the muscle fiber itself. LGMD2C is clinically characterized by progressive weakness that mainly affects the limb-girdle muscles. Hypertrophy of the calf muscles and macroglossia (an enlarged tongue) are frequently observed. The first symptoms appear at 3-5 years of age in the most severe forms and at 10-40 years of age in the mildest forms. Populations in the Mediterranean basin (northern Africa) and gypsies living in Europe are particularly affected. At present, there is no curative treatment for this muscular dystrophy.

For more information:

Source: A phase I trial of adeno-associated virus serotype 1-gamma-sarcoglycan gene therapy for limb girdle muscular dystrophy type 2C - Brain 2012; doi: 10.1093/brain/awr342, published on January 11, 2012 and available on this link:

<http://brain.oxfordjournals.org/cgi/reprint/awr342?ijkey=jz7sxUCEa0w0jpv&keytype=ref>

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About the AFM

The French Muscular Dystrophy Association (AFM) federates patients with neuromuscular diseases (genetic diseases that kill, muscle after muscle) and their parents. Thanks in great part to donations from France's annual Telethon (€90 million in 2010), the AFM has become a major player in biomedical research into rare diseases in France and worldwide. It is currently funding 36 clinical trials on 31 different genetic diseases affecting the eyes, the blood, the brain, the immune system, the muscle... Thanks to its Généthon research lab, the AFM stands out through its unique ability to produce and test its own gene-based medicines.

More information at www.afm-telethon.fr

About Généthon

Created by the French Muscular Dystrophy Association (AFM), Généthon is funded almost exclusively by donations from France's annual Telethon. Its goal is to deliver innovative gene therapies to patients. After having played a pioneering role in deciphering the human genome, with over 200 scientists, physicians, engineers and regulatory affairs specialists, Généthon is one of the world's leading centers for preclinical and clinical research and development in the field of gene therapy for rare diseases. Généthon also has a biomanufacturing platform for clinical-grade vectors, that will open in Evry in 2012, the world's largest facility for pre-industrial pilot production (Généthon BioProd). www.genethon.fr

About the Institut de Myologie

The *Institut de Myologie* is located at Pitié-Salpêtrière University Medical Center in Paris. It was founded in 1996 by the AFM, in collaboration with the AP-HP public hospitals group, the INSERM French national institutes of health, Pierre and Marie Curie University, the CEA Atomic Energy Commission and the CNRS national research institute (since 2009, in the latter case). It brings together almost 300 expert physicians, researchers and engineers in the field of myology and is an international center of excellence for the diagnosis, study and treatment of neuromuscular diseases, the generation of basic scientific knowledge and novel therapeutic approaches (including biotherapies) and the organization of clinical trials. At present, 31 clinical studies are being run at the Institute.

About the AP-HP

The *Assistance Publique-Hôpitaux de Paris* (AP-HP) is the University medical center of the Paris-Ile de France region. In this respect, it provides comprehensive medical care while running the research and teaching projects that will shape the medicine of the future. The AP-HP exports its expertise in medicine, hospital care and other aspects of healthcare worldwide. The group comprises 37 hospitals (including 3 outside Paris) and a home care organization.

Key figures:

- 7 million patients treated each year, including 1 million in the emergency room.
- over 2700 collaborative research projects (800 of which are led by the AP-HP) and over 26,000 patients enrolled in clinical trials.
- 3,000 interns and 13,000 medical students and students in other healthcare-related sectors.

About the UPMC

The *Université Pierre et Marie Curie* (UPMC, Pierre and Marie Curie University) is the top-ranked French university and number 8 in Europe (according to the Taiwan Academic Ranking of Universities). The UPMC is the largest scientific and medical university complex in France. All the major scientific and medical disciplines are covered at the university's 18 locations: chemistry, electronics, computer science, mathematics, mechanical engineering, physics, the earth and environmental sciences, life science and medicine. Along with Pantheon-Assas Paris 2 University and Sorbonne Paris 4 University, the UPMC is a founder member of the "Sorbonne Universities" scientific cooperation foundation.

Key figures for the UPMC: a university community of 10,500 UPMC and seconded staff, including 8,200 in research; 32,000 students, including 7,000 foreign students; 2,000 masters graduates each year; 250 engineering graduates each year; 126 labs; 3,400 graduate students and 800 PhD theses each year. The university also encompasses the elite Polytech Paris UPMC engineering school.

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