



PRESS RELEASE

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Effectiveness of innovative gene therapy treatment demonstrated in canine model of Duchenne muscular dystrophy

*A collaboration involving three laboratories supported by the AFM-Telethon, Atlantic Gene Therapies (AFM-Telethon, Inserm UMR 1089, Université de Nantes, Nantes University Hospital), Généthon (Evry) and the Institute of Myology (Paris), demonstrated the effectiveness of an innovative gene therapy treatment in the canine model of Duchenne muscular dystrophy. This work, published in the journal *Molecular Therapy* in November, was mainly financed by French Telethon donations. It paves the way for a clinical trial in humans.*

Duchenne muscular dystrophy is the most common neuromuscular disease of children (affecting 1 boy in 3500-5000 births). It is caused by a genetic defect in the DMD gene residing on the X chromosome, which results in the absence of the dystrophin protein essential to the proper functioning of muscles.

The treatment being developed by researchers at **Atlantic Gene Therapies, Généthon** and the **Institute of Myology**, is based on the use of an AAV vector (Adeno Associated Virus) carrying a transgene for the skipping of a specific exon which allows functional dystrophin production in the muscle of the patient.

Safety, efficacy and stability of the treatment in dogs

In GRMD (Golden Retriever Muscular Dystrophy) dogs the treatment aimed at skipping exons 6, 7 and 8 of the dystrophin gene. The product was given by loco-regional administration in the forelegs of 18 dogs who were followed for 3.5 months after injection. It was well tolerated by all treated dogs; **no immune response against the synthesized dystrophin was observed**. Exon skipping resulted in high levels of expression of dystrophin in the treated muscles. The results of this treatment also indicate that, **once injected into the muscle tissue a prolonged and stable effect is produced over the observation time of the study** and, unlike antisense oligonucleotides already used clinically for exon skipping, it does not need to be re-administered regularly. The synthesis of "new" dystrophin is dependent on the dose of vector injected: the higher the dose, the greater the exon skipping is effective. Muscle strength also increases with dose. **80% of muscle fibers expressed the "new" dystrophin at the highest dose**. This is a very encouraging result

because a minimum of 40% of dystrophin in muscle fibers is believed to be necessary for the muscle force to be significantly improved.

A phase I/II clinical trial phase

These results open the way for a phase I / II clinical trial by loco-regional administration in the upper limb of non-ambulatory Duchenne muscular dystrophy patients which are amenable to treatment by the specific skipping of exon 53. The regulatory toxicology and biodistribution studies have just ended and the filing of an application with regulatory authorities is planned for 2015.

Atlantic Gene Therapies, Genethon and **the Institute of Myology are members of the Institute of Biotherapy for Rare Diseases created by the AFM-Telethon**. With over 600 experts in Nantes, Paris and Evry it is a unique and potent force for the development of gene therapies for rare diseases.

This work also received funding under the ADNA (Advanced Diagnostics for New Therapeutic Approaches) program which is dedicated to the development of personalized medicine and supported by the Public Investment Bank.

Publication : Forelimb Treatment in a Large Cohort of Dystrophic Dogs Supports Delivery of a Recombinant AAV for Exon Skipping in Duchenne Patients

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About AFM-Téléthon - www.afm-telethon.fr

The French Muscular Dystrophy Association (AFM) federates patients with neuromuscular diseases (genetic diseases that causing progressive irreversible muscle atrophy lead to death) and their parents. Thanks in great part to donations from France's annual Telethon (€89,3 million in 2013), the AFM-Telethon has become a major player in biomedical research for rare diseases in France and worldwide. It currently funds 34 clinical trials in different genetic diseases affecting the eye, blood,

brain, immune system, and muscles... Thanks to its Genethon research lab, the AFM-Telethon stands out through its unique ability to produce and test its own gene-based medicines.

About Généthon - www.genethon.fr

Created and funded by the AFM-Telethon, Généthon's mission is to make available to patients innovative gene therapy treatments. Having played a pioneering role in deciphering the human genome, Généthon is today, with more than 200 scientists, physicians, engineers and regulatory affairs specialists, an international research and development center for preclinical and clinical gene therapy treatments for rare diseases. Généthon also has the largest site in the world for GMP production of gene therapy products, Généthon Bioprod. Généthon received the 2012 Prix Galien for Pharmaceutical Research (France) and was thus the first non-profit laboratory to receive this prestigious award.

About Atlantic Gene Therapies - www.atlantic-gene-therapies.fr

Created in 2012 under the leadership of the AFM-Telethon, Atlantic Gene Therapies has the capacity to support projects from research through clinical trials thanks to its expertise and dedicated translational research platforms. 85 experts from this Nantes center develop these gene therapy strategies including notably genetic diseases of the retina, muscles and central nervous system.

About the Institute of Myology - www.institut-myologie.org

Established in 1996, the Institute of Myology is located in the heart of the Paris Pitié-Salpêtrière hospital. Its 280 physicians, scientists, engineers and nurses provide basic and clinical research activities, medical consultations for patients with neuromuscular diseases and a teaching activity. It is an international center of excellence for clinical trials in neuromuscular diseases.

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