PRESS RELEASE

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48th Annual Meeting of the ESPGHAN

Evidence of efficacy of gene therapy in rodents affected by a rare genetic liver disease, Crigler-Najjar syndrome

Federico Mingozzi, head of the Immunology and Liver Gene Therapy team at Généthon, the laboratory created by the AFM-Téléthon, presented at the 48th Annual Meeting of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN, May 6-9, Amsterdam), work done in collaboration with an Italian and Dutch teams showing long-term correction of a genetic defect causing toxic buildup of bilirubin in murine and rat models of Crigler-Najjar syndrome.

Crigler-Najjar syndrome is a rare autosomal recessive disorder caused by mutations in the UGT1A1 gene, which result in the toxic accumulation of bilirubin, a substance made by the liver in the body. Indeed, when the UDP-glucuronosyltransferase 1 isotype A1 (UGT1A1), the enzyme responsible for removing bilirubin, doesn't work, the substance accumulates, causing a severe and chronic jaundice, and becoming toxic for the brain and leading to lethality.

Gene therapy has allowed the restoration of an equivalent level of bilirubin to those found in healthy animals

Federico Mingozzi team (Généthon, Evry/France), in collaboration with the team of Andres Muro (ICGRB, Trieste/Italy) and the team of Piter Bosma (AMC, Amsterdam/Netherlands), transferred with an AAV vector (adeno-associated virus), developed by Généthon, a copy of the UGT1A1 gene (coding for the production of the UGT1A1 enzyme) in liver cells (hepatocytes) of rats and mice carriers of the anomaly. After injection, levels of bilirubin in the treated animals became equivalent to those of healthy animals. The correction was confirmed more than 6 months after gene therapy, without requiring prior immunosuppression or additional intervention.

The researchers demonstrated that a single injection of the AAV vector-UGT1A1 enabled the long-term correction of the Crigler-Najjar syndrome in the treated animals.

Towards a phase I/II clinical trial

These results open the way to the establishment of a phase I/II clinical trial by the end of 2016, of which Généthon will be the promoter. In 2015, regulatory toxicity studies and industrial transposition for the production of clinical batch processing under GMP (Good Manufacturing Practices) will take place at Généthon*. Twenty patients will be enrolled in 5 clinical centers in Europe: in France (APHP Antoine Béclère), the Netherlands (Academic Medical Center), Germany (Hannover Medical School), and Italy (Azienda Ospedale Papa Giovanni XXIII in Bergamo and Federico II Hospital in Naples).

Federico Mingozzi, driver for this work: "These promising results allowed us to start thinking about clinical trial, which hopefully will start by the end of 2016 or early 2017. I am very excited to continue this project, which finds its strength in all the participating actors - the researchers, the clinical investigators, and the patients' associations of France, Italy, and the Netherlands. Everyone has been working very hard together with the Genethon team since 2013."

Frédéric Revah, CEO of Généthon: "This new trial will be a new challenge for Généthon. Indeed, after undertaking the development of gene therapy treatments for immune deficiencies, for diseases of the muscle and contributing to the development of treatments for diseases of the vision and blood, Généthon will begin the development of a drug candidate targeting the liver. A new exciting project for Généthon and its unique expertise: develop and simultaneously produce gene therapy treatments for different families of orphan diseases."

These results were presented May 7, 2015 at the plenary session 10:30 (http://www.espghan2015.org/programme/).

The Crigler-Najjar syndrome

The Crigler-Najjar syndrome is an inherited disorder of bilirubin metabolism characterized by high serum levels of unconjugated hyperbilirubinemia due to hepatic deficit of bilirubin glucuronosyltransferase activity. Many mutations of UGT1A1 gene (2q37) are responsible for a partial or total loss of the activity of the enzyme, resulting in a more or less significant decrease in the conjugation of bilirubin. The complete absence of enzymatic activity of UGT1A1 causes the most severe form of Crigler-Najjar syndrome. Severe Crigler-Najjar patients survive only through very restrictive daily treatment by phototherapy (10 to 12 hours per day) or have to undergo liver transplantation. Milder forms of the disease, resulting from only a partial loss of UGT1A1 activity in liver, can be treated with phenobarbital alone or in combination with phototherapy.

The syndrome is characterized by an intense and chronic jaundice causing yellowing of the skin and of the the eyes. Jaundice can become toxic to the brain, causing severe neurological disorders that can lead to the death of patients. The disease is extremely rare with an annual incidence of 1/1 000 000 births.

About Généthon - www.genethon.fr

Created by the AFM-Téléthon, 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 has the largest site in the world for GMP production of gene therapy products, Généthon Bioprod. In 2012, Généthon was the first associative laboratory to receive the 2012 Prix Galien for Pharmaceutical Research (France). As part of a therapeutic program on genetic diseases of the blood and immune system, Généthon working for over 10 years on gene therapy of Wiskott-Aldrich syndrome. The laboratory is currently conducting clinical trials for this disease in Europe, Paris and London, and the United States with the Children's Hospital Boston. *Généthon has one of the largest GMP production sites of gene therapy drugs in the world, Généthon Bioprod. In 2012, Généthon has received the prestigious Prix Galien for Pharmaceutical Research (France) and in 2015 Généthon was one of 16 winners of the Global Innovation Competition 2030 for its industrial process development work for vectors gene therapy.

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