NEWSLETTER

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CEO COMMENTARY

ARTIFICIAL INTELLIGENCE MAY HELP IMPROVE EFFECTIVENESS OF GENE THERAPIES ALONG WITH PATIENT ACCESS

Frederic Revah, CEO, Genethon

The emergence of technologies based on artificial intelligence (AI) is revolutionizing drug discovery and holds many promises in the field of gene therapy. At Genethon, we have multiple examples of how these technologies can be used to develop products that are more efficient and safer with improved production technologies.

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INSIDE

Genethon uses AI to improve AAV capsids. While several AAV-based gene therapy products have already obtained market authorization for the treatment of rare and common diseases, development of these complex therapies continues to face major scientific and technical hurdles.

The use of AAV vectors has limitations, such as natural immunization of 30% to 40% of the population and difficulty in targeting a specific tissue. In this context, the use of AI solutions stands out as a deciding factor to overcome these obstacles and produce optimized vectors that better target the relevant tissues, have an improved biodistribution and make it possible to inject smaller quantities of product while maximizing the therapeutic effect.

Genethon partnered in 2021 with Whitelabs Genomics, a company which has developed the proprietary Catalyst™ platform enabling the multi-parametric analysis of complex biological data. The partnership has the primary objective of harnessing the Catalyst™ platform to develop next-generation gene therapy vectors, enhancing their precision regarding the tissues to be treated while reducing their immunogenic potential, and other possible side effects. This promising collaboration is ongoing and covers both the creation of proprietary AI tools specifically tailored for our specific objectives and the generation of innovative AAV capsids.

On the manufacturing side, Genethon is collaborating with Thales, a European leader in AI for mission-critical systems for Defense, Security, Aeronautics, Space and Cybersecurity. Our collaboration focuses on AI tools for improving bioproduction efficiency.

Producing gene therapy treatments is an extremely, complex, time-consuming, and particularly costly process. Major challenges include reducing the production time and costs. To improve the productivity and the quality of gene therapy products, the objective of this collaboration is to develop first of its kind efficient digital models for increasing bioproduction yields in the field of gene therapy.

Genethon and Thales are working together to develop a digital model that uses AI to model bioproduction processes and optimize yields. This should ultimately allow us to decipher the impact of certain production parameters on productivity and the quality of the bio-drugs without having to resort to systematic experimentation.

This project is in line with our objective of improving production yields and thus reducing the production costs of innovative gene therapy drugs, which for certain diseases can reach several hundreds of thousands of euros per patient. The use of AI thus serves our global goal of guaranteeing access for patients to these innovative treatments.

The Genethon Team gathers at the recent European Society for Gene & Cell Therapy Conference in Brussels October 24-27

PRODUCT DEVELOPMENT

Atamyo Therapeutics Announces Major Milestones in Development of Gene Therapies for Limb-Girdle Muscular Dystrophies

Atamyo Therapeutics, a spinoff of Genethon, announced significant progress in its efforts to bring next generation safe and effective gene therapies to patients with limb-girdle muscular dystrophies (LGMDs).

LGMDs are rare genetic conditions causing progressive atrophy and weakness in shoulder and hip muscles that can spread to other parts of the body.

In early September 2023, the U.S. Food & Drug Administration (FDA) cleared the company's Investigational New Drug (IND) application for a Phase 1b/2a clinical trial in the US of ATA-100, a gene therapy for fukutin-related protein (FKRP) limb-girdle muscular dystrophy Type 2I/R9 (LGMD2I/R9). ATA-100 (formerly known as GNT0006) currently is being evaluated in a multi-center phase 1b/2b in Denmark, France, and United-Kingdom. **Read more.**

Also in September, Atamyo filed a Clinical Trial Application (CTA) in Europe for ATA-200, its gene therapy targeting γ-sarcoglycan (SGCG) related limb-girdle muscular dystrophy Type 2C/R5 (LGMD2C/R5). In addition, to support development of ATA-200 the company announced non-dilutive financing up to €8m from France 2030, a government program managed by Bpifrance. **Read more.**

Atamyo leverages unique expertise in AAV-based gene therapy and muscular dystrophies from the Progressive Muscular Dystrophies Laboratory at Genethon.

Stephane Degove, Co-Founder and Chief Executive Officer of Atamyo, said "The ongoing clinical trial in LGMD 21/R9 and the initiation of the clinical program for LGMD2C/R5 confirms our unique capabilities in bringing to patients suffering from limb-girdle muscular dystrophies a new generation of safe and effective gene therapies."

Gene Therapy Pioneer Roger Hajjar, MD, Joins Atamyo Board of Directors

Atamyo also announced the appointment of Roger Hajjar, MD, Director of the Gene and Cell Therapy Institute at Mass General Brigham in Boston, to its Board of Directors.

Dr. Hajjar is a gene therapy pioneer and internationally recognized scientist with more than 500 peer-reviewed publications. His cardiac gene therapy discoveries and methodologies for cardiac-directed gene transfer are currently utilized by investigators worldwide.

"We are thrilled to have Roger's stature and experience join our Board," said Stephane Degove. "His outstanding scientific, medical, and entrepreneurial experience in cell and gene therapy will be invaluable as we progress the development of our gene therapies for both Limb-Girdle Muscular Dystrophies and cardiomyopathies." **Read more.**

RESEARCH COLLABORATIONS

Genethon, Thales Collaborate on Artificial Intelligence Tools for Improving Bioproduction Efficiency

Genethon and Thales, a European leader in artificial intelligence for mission-critical systems, are combining their know-how to develop efficient digital models for improving bioproduction yields in the field of gene therapy.

"This project is in line with our objective of improving production yields and thus reducing the production costs of innovative therapy drugs, which can reach several hundreds of thousands of euros per patient. This is a major challenge for guaranteeing access for patients to these treatments," said Genethon CEO Frédéric Revah.

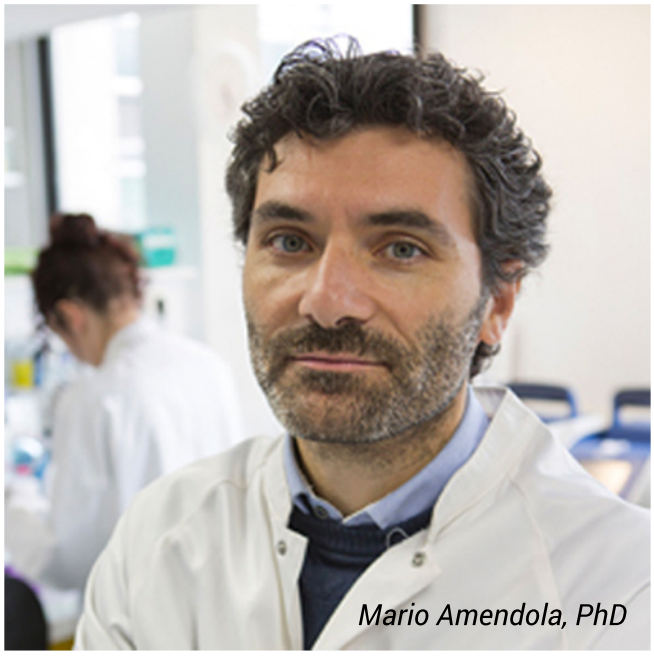
Lilian Seigneur, Manager of the Healthcare-Public Sector Business Unit for Thales Digital Services, added, "This collaboration between Genethon and Thales is a source of great pride for our teams. We are putting our expertise in Artificial Intelligence applied to healthcare and our ability to innovate into this great project to improve bioproduction yields. This completely unprecedented project binds the worlds of research, industry and digital services to deliver joint innovative solutions." **Read more.**

Genethon Experts Participate in the MAGIC Consortium To Develop Therapeutic Strategies for Muscular Dystrophies

The international project, described as the Next-generation Models And Genetic theraples for rare neuromusCular diseases (MAGIC), is a four-year (2023-2027) initiative with the goal of transforming the treatment landscape for muscular dystrophies. The consortium is funded by Horizon Europe and UK Research and Innovation.

Led by Prof. Francesco Saverio Tedesco (University College London / Francis Crick Institute) with the support of Mario Amendola (Inserm/Genethon), the MAGIC project brings together 15 partners from nine countries.

In addition to Dr. Amendola, who is the head of Genethon's Gene Editing Laboratory, two other scientists from Genethon's Immunology and Liver Diseases Laboratory are participating: Giuseppe Ronzitti, head of the laboratory, and David-Alexandre Gross. **Read more.**



Mario Amendola, PhD

SCIENTIFIC PUBLICATIONS

CEO Frederic Revah, in *Scrip* Interview, Discusses Development of Crigler-Najjar Syndrome Gene Therapy and Challenges for Commercialization

Scrip, a US publication of Citeline, interviewed Genethon CEO Frederic Revah to discuss the non-profit organization's positive Phase 1/2 clinical trial data of GNT-0003, a gene therapy for Crigler- Najjar syndrome. The clinical research is featured in the August 17, 2023, issue of the *New England Journal of Medicine.*

Crigler-Najjar, a rare liver disease, is characterized by hyperbilirubinemia and caused by a deficiency in the liver enzyme UGT1A1. The trial data demonstrate the possibility of restoring expression of the enzyme with GNT-0003. The gene therapy combines an AAV8 vector with a normal copy of the UGT1A1 gene coding for the bilirubin metabolizing enzyme. **Read more about the clinical trial in Genethon's press release.**

In the *Scrip* article, Dr. Revah also discussed the challenges in commercializing gene therapies for rare diseases. He noted a **pivotal study of GNT-0003** is underway to confirm the Phase 1/2 results. If successful, Genethon will be able to apply for product licensing in the EU. At that point, Dr. Revah suggested Genethon may want to create a standalone spin-off company to commercialize the gene therapy. **Read more of Dr. Revah's interview in the *Scrip* article** (Subscription required.)

The Phase 1/2 trial results published by the *New England Journal of Medicine* in an article titled, **"Gene Therapy in Patients with the Crigler–Najjar Syndrome,"** demonstrated GNT-0003 lowered bilirubin levels below the toxic threshold with a single intravenous injection. The data also confirmed the safety and tolerance of the treatment for all patients in the study. Three patients, treated with the highest dose, have been able to stop using phototherapy for the last 18 months or more. This is the first proof of the efficacy of a gene therapy in a metabolic disease of the liver.

Sonia Albini, PhD, R&D Scientist, Genethon

Research on Dual AAV Approach for Duchenne Muscular Dystrophy Published in the *International Journal of Molecular Sciences*

Duchenne Muscular dystrophy (DMD) is caused by the lack of dystrophin, a muscle protein essential for the integrity of muscle fibers.

Gene therapy for DMD, employing the adeno-associated virus (AAV), faces the challenge imposed by the limited packaging capacity of AAV. In therapeutic strategies currently implemented, researchers use a short version of dystrophin (µDys), which presents limitations due to its reduced size.

Genethon's Sonia Albini, a researcher on the Progressive Muscular Dystrophies team led by Isabelle Richard, developed a dual AAV vector approach for the expression of a larger dystrophin version. **Read more.**

The research has been awarded funding from BPIFrance as part of the French government's France 2030 initiative.

"This funding gives us the opportunity to confirm and optimize the efficacy of the gene therapy product we have developed, based on the generation of a therapeutic gene that is more complete and more efficient than the one currently used in clinical trials, combined with a new vector developed to more specifically target skeletal and cardiac muscle," said Dr. Albini.

Genethon Announces Publication in *The Lancet Neurology* of Clinical Trial Results of a Gene Therapy for Myotubular Myopathy, a Severe Muscle Disease

Genethon announced *The Lancet Neurology* published **online** preliminary results of a clinical trial conducted by Astellas Pharma using a gene therapy developed by Genethon for X-linked myotubular myopathy, a rare genetic muscle disease affecting 1 in 50,000 newborn boys.

Myotubular myopathy is caused by mutations in the MTM1 gene encoding myotubularin, a protein involved in muscle cell function. Characterized by extreme muscle weakness and severe respiratory distress, 50% of affected children die before age 18 months and 75% die before age 10. The gene therapy uses an adeno-associated viral vector (AAV8) to deliver a copy of the MTM1 gene.

> *"These clinical results show both how spectacularly effective gene therapy can be, and the challenges that remain, particularly in terms of side effects in certain contexts."*
>
> *-- Frederic Revah, Genethon CEO*

Of 24 children enrolled in the ASPIRO trial, conducted in France, Germany, Canada and the U.S., 16 of them can now breathe without assistance, 12 stand up on their own, and 8 can walk. The trial has been paused for an investigation into the origins of the complications responsible for the deaths of 4 children, who showed signs of pre-exiting hepatobiliary pathology.

"These clinical results show both how spectacularly effective gene therapy can be, and the challenges that remain, particularly in terms of side effects in certain contexts," said Frederic Revah, Genethon CEO. "While our teams are already committed to understanding and anticipating these issues, the knowledge gained from this clinical trial, which highlights certain limitations and particular hepatic susceptibilities, is rich in lessons for the entire scientific community."

Ana Buj-Bello, Director of Research at Inserm and head of Genethon's Neuromuscular Diseases and Gene Therapy team, designed the gene therapy. She is one of the authors on *The Lancet Neurology* **article** and co-authored the preclinical work that led to the ASPIRO trial.

> *"It took years of research to imagine, design and demonstrate the efficacy of the gene therapy for this very severe and complex disease."*
>
> *-- Ana Buj-Bello, Genethon*

Dr Buj-Bello remarked, "I've devoted my entire career working on myotubular myopathy. It took years of research to imagine, design and demonstrate the efficacy of the gene therapy for this very severe and complex disease. Even though we absolutely must understand the reasons for the adverse effects observed in this clinical trial, it is exceptional to see children who were known to be doomed make incredible progress thanks to this drug candidate." **See the video of one patient's progress in France.** This patient was treated at I-Motion, the Institute of Myology's French pediatric clinical trials center:

Genethon entered an agreement with Audentes Therapeutics in 2014 for the preclinical development of the gene therapy. Astellas acquired the gene therapy in 2019 with the company's acquisition of Audentes.

Celine Contet Joins Genethon as Communication Manager

Celine Contet recently joined Genethon as Communication Manager after serving nine years in various communications positions with LEO Pharma, a Danish multinational pharmaceutical company.

Ms. Contet is a graduate of Sorbonne Nouvelle and has a communication master's degree from UPEM (University of Marne-La Vallée). She began her career as a communicator for different companies such as Orange, Sofrecom and Edenred before joining LEO Pharma in 2014 where she successively held positions as Internal Communication Officer, Internal Communication Manager and then Communication Manager.

Among her responsibilities at Genethon, Ms. Contet will provide management for communications and information dissemination, develop media relations in US, and plan special events and projects in collaboration with the AFM-Téléthon communication team.

"For me, joining Généthon is an opportunity to pursue my career in a unique place, with a strong legacy, where I hope I can bring all my energy and expertise to overcome the challenges we face to be recognized as a leader in gene therapy and help patients with rare diseases," Ms Contet said.

"I love being in contact with different people, using different ways of communicating," she added. "There are so many opportunities to communicate, to be creative and to try out different approaches to achieve strategic objectives. Working in communication is a non-linear area which means you must adapt and change the message continually to meet target needs."

Genethon and Atamyo Therapeutics Featured in Scientific Conferences

Product development and scientific advances of Genethon and its spinoff company, Atamyo Therapeutics, were featured in conferences this fall in Europe and the U.S.

Presentation of the first clinical results of Atamyo's ATA-100 gene therapy for fukutin-related protein limb-girdle muscular dystrophy Type 2I/R9 were presented at two conferences in October 2023: the 30th Annual Congress of the European Society of Gene & Cell Therapy (ESGCT) in Brussels; and the 2023 International Limb-Girdle Muscular Dystrophy Conference in Washington, DC.

"These first results, in particular those related to transgene expression in muscle fibers are really exciting" said Dr. Sophie Olivier, Atamyo's Chief Medical Officer. "With the DSMB clearance to start the 2nd cohort, we are looking forward to enrolling new patients in Europe and the US."

ATA-100 is being evaluated in a multi-center phase 1b/2b in Denmark, France, and the United Kingdom, and has received IND clearance by FDA. **Read more.**

Genethon's latest advances in gene therapy research, product development and bio-manufacturing were featured in 3 oral and 11 poster presentations at the ESGCT conference. "The breadth of this significant research is testament to the growth in importance of gene therapy in modern medicine," said Frederic Revah, Genethon CEO. **Read more.**

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