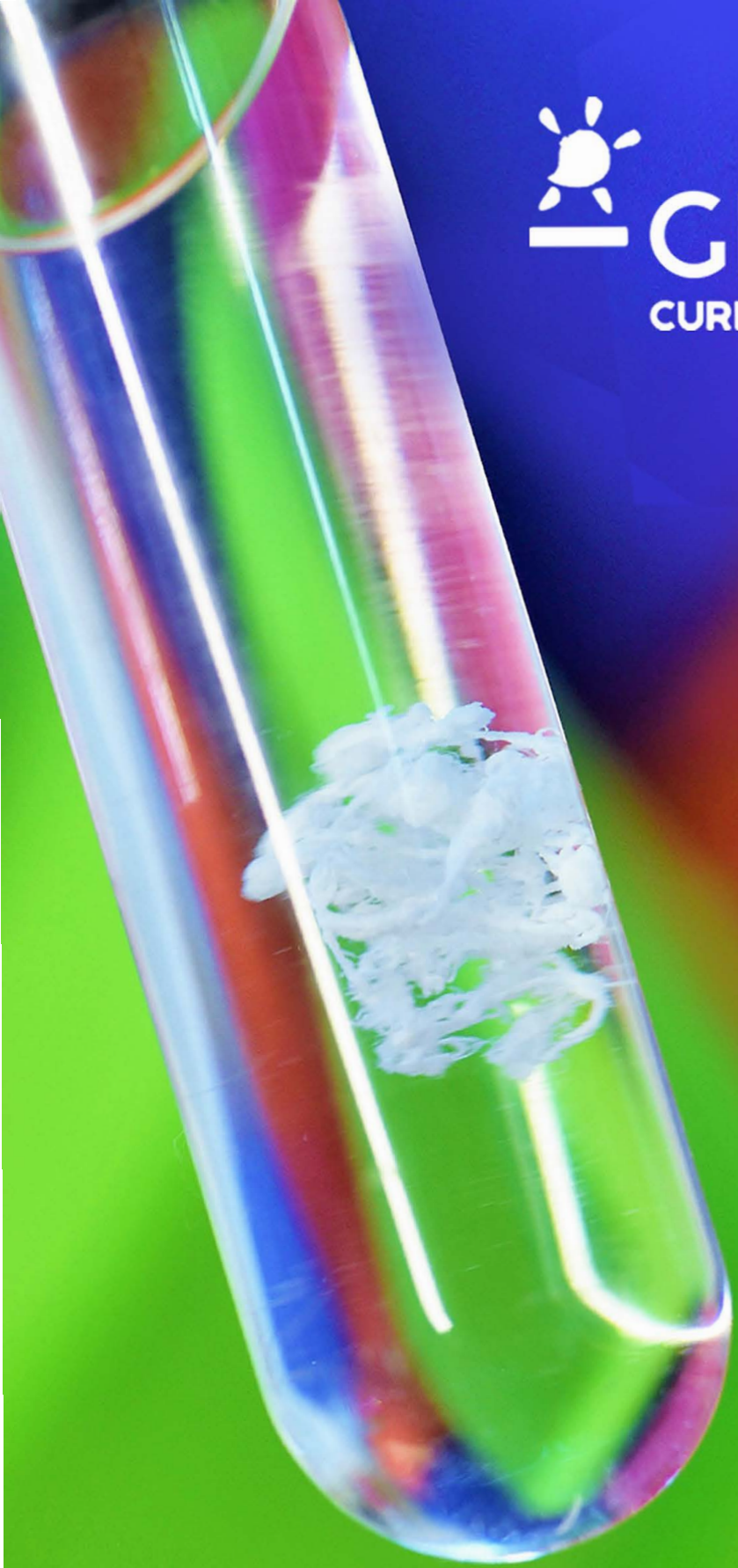


GENETHON

CURE THROUGH INNOVATION

2025 Issue Number 1

NEWSLETTER

CEO COMMENTARY

AAV Vectors a Key to Gene Therapy Success - but not the only one

Over the past three decades Genethon has strengthened adeno-associated viral vectors as a pivotal tool in delivering gene therapies, achieving remarkable clinical successes. We are continuously working to increase safety, efficacy and disease applications with advances in our AAV platform such as improved vector delivery efficiency and organ targeting, management of immune response and reduction in production costs.

Among the most recent successes from our R&D are clinical trials for Duchenne muscular dystrophy (DMD) and Crigler-Najjar syndrome along with two forms of limb-girdle muscular dystrophy from Atamyo Therapeutics, a Genethon spin-off company.

Our DMD gene therapy (GNT0004) is Phase 3 ready and exemplifies scientific breakthroughs yielding the potential of succeeding in bringing a therapy with enhanced clinical efficacy.

To address DMD we engineered a recombinant AAV8-based vector delivering a microdystrophin gene, and effective at doses significantly lower than other products developed along similar lines. Combined to the sustained efficacy observed at 2-year follow up in the first patients treated, our results point to GNT0004 as a potential best-in-class DMD gene therapy. See **Global Genes podcast.**

To broaden these new advanced applications to rare diseases we are developing a next generation of gene therapies, improving safety and efficacy while lowering production costs through technological advances in our AAV platform.

We are using artificial intelligence to create AAV vectors for more accuracy in targeting skeletal muscle to treat more neuromuscular diseases with lower doses of vector. With existing vectors some of these diseases require large doses of AAVs and many do not reach the target cells, causing adverse effects. **Read more.**

Frederic Revah, CEO of Genethon

We are also developing a dual AAV vector approach to increase packing capacity of normal copies of mutated genes whose coding sequence is greater in length than 4.5 kilobase pairs, the maximum capacity of one AAV. Delivering a longer copy of a normal gene increases the therapeutic benefit for many diseases. **Read more.**

To lower high production costs, Genethon is exploring multiple avenues, including, through collaborating with Samabriva, applying plant-based production of AAV vectors with a goal of reducing gene therapy prices for patients. **Read more.**

Another critical barrier is managing AAV immune response. Thirty percent of patients are naturally immune to certain vectors. We are collaborating with Hansa Biopharma on a Phase 2 trial to determine if imlifidase, an antibody cleaving enzyme, can breakdown the anti-AAV antibodies that prevent gene therapies from working. **Read more.**

Remaining at the forefront of developing gene-based medicines also implies keeping eyes widely open on alternative delivery methods. We are actively exploring non-viral based delivery systems, in particular Lipid Nano Particles (LNPs). Although these approaches may not for now substitute for AAVs in muscle delivery, they represent strong potential for gene editing approaches for multiple other organs of interest.

These breakthroughs move us closer to treating all rare disease patients. Explore the full range of our work **on our website.**

SCIENTIFIC PUBLICATIONS

Long-Term Success of Gene Therapy in Patients with Fanconi Anemia

Results of a clinical trial conducted by Rocket Pharmaceuticals and the Spanish CIEMAT, in collaboration with Genethon, which helped design and develop the drug vector used in the trial, have demonstrated for the first time the efficacy and safety of gene therapy in patients with Fanconi anemia, a rare blood disorder.

These results, published in *The Lancet,* December 3, 2024, are the fruit of over 20 years' research and 7 years' patient follow-up.

Anne Galy, PhD, Director of ART-TG and former Director of the Inserm Joint Research Unit (UMR S951) at Genethon, said, "The publication of the work in *The Lancet* is the culmination of lengthy efforts coordinated by our Spanish colleagues to improve every stage of the Fanconi anemia gene therapy protocol, in order to obtain a significant graft of corrected blood stem cells in patients. The quality of the purified lentiviral vector we had developed at Genethon and which was produced at Yposkesi was an important factor in this process, due to its lack of toxicity on very fragile stem cells." **Read more.**

PRODUCT DEVELOPMENT

2-Year Post-Treatment with Duchenne Muscular Dystrophy Gene Therapy Shows Motor Function Stabilization, Significant Reduction in CPK Levels

In addition to maintenance of motor function, the data revealed the gene therapy was well tolerated and patients experienced significant reduction levels of creatine phosphokinase (CPK), a biomarker of muscle damage, with an average decrease of more than 75% at 18 months in three patients.

Genethon presented the 2-year follow-up data from the dose escalation portion of a combined Phase 1/2/3 trial of its gene therapy, GNT0004, at the American Society of Gene & Cell Therapy's annual meeting, May 13-17, in New Orleans.

In this phase of the study, five patients, aged 6 to 10 years, were treated; two at the first dose level and three at the second dose level ($3x10^{13}$ vg/kg) in an effort to select the optimal dose for the pivotal trial planned for this year in Europe and the US.

"The results," observed CEO Frederic Revah, "are very positive in patients treated at the dose of $3x10^{13}$ vg/kg, both in terms of microdystrophin expression and clinical efficacy criteria. Besides these results, the advantage of our product lies in the selected dose for the pivotal phase, which is lower than those used in other gene therapy trials for Duchenne muscular dystrophy. We are currently preparing the pivotal phase that we will conduct in Europe and the US." ***Read more.***

Atamyo Therapeutics Achieves Significant Milestones in Clinical Trials of Gene Therapies for Two Subtypes of Limb-Girdle Muscular Dystrophy

Genethon spin-off Atamyo Therapeutics in April completed the dose-escalation phase of a Phase 1b/2b clinical trial in Europe of ATA-100 for limb-girdle muscular dystrophy Type 2I/R9 (LGMD2I/R9) and announced in June dosing in the US of the first two patients in a Phase 1b/2 study of ATA-200 for LGMD2C/R5, a second subtype of limb-girdle muscular dystrophy.

Both subtypes of this rare children's disease, caused by different genetic mutations, lead to loss of ambulation with other serious complications and there are no cures. ATA-100 and ATA-200 gene therapies were awarded Orphan Drug Designations in the US and Europe. ATA-100 and ATA-200 received Rare Pediatric Disease Designations in the US; and ATA-100 was granted Fast Track Designation in the US.

In the ATA-100 study, the Independent Data Safety Monitoring Board stated the safety in the dose-finding phase showed no concern and that both ATA-100 doses could be selected for the Phase 2b part of the trial, without any changes to be made to the protocol.

"ATA-100 is the first treatment in LGMD-2I/R9 to present improvements in all functional endpoints in all patients treated," said Atamyo CEO and Co-Founder Stephane Degove. **Read more.**

For treatment of LGMD2C/R5, the deployment in the US of Atamyo's trial of ATA-200 is funded by **The Dion Foundation for Children with Rare Diseases.** This study has also received regulatory clearance in France and Italy.

The Phase1b/2 open-label dose escalation study **(NCT05973630)** will evaluate safety, pharmacodynamics, efficacy, and immunogenicity of ATA-200. The first two patients were dosed at the University of Florida in Gainesville.

"LGMDR5 is the most severe form of LGMDs with onset of symptoms during childhood and a phenotype close to Duchenne muscular dystrophy," said Atamyo Chief Medical Officer Dr. Sophie Olivier. "We are thrilled to propose a potentially disease-modifying treatment to these young patients." **Read more.**

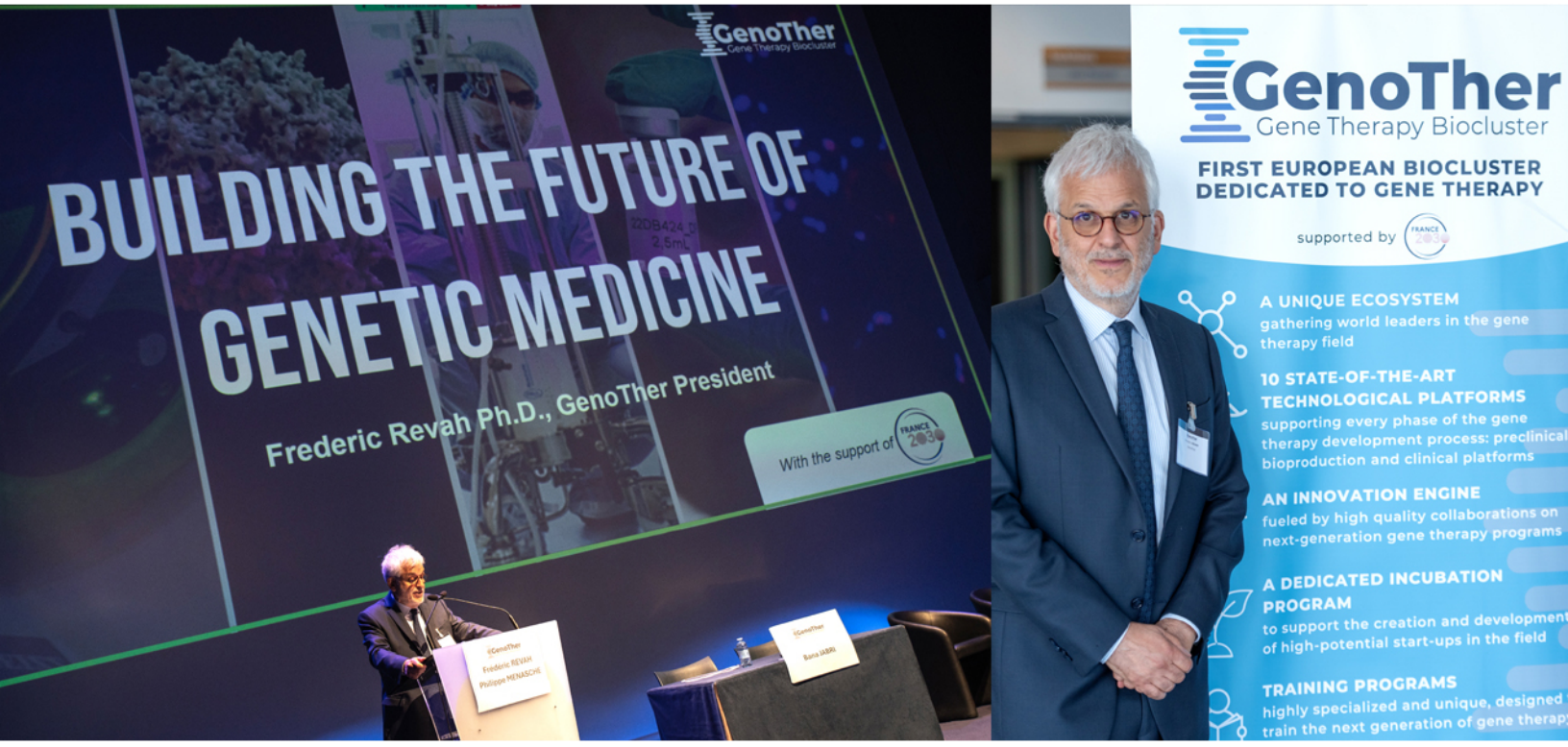
GenoTher, France and Europe's Unique Public-Private Gene Therapy Biocluster, Holds Its First Summit on Efforts to Accelerate Treatments for Genetic Diseases

GenoTher Biocluster held its first international summit. On this occasion, more than 20 international speakers (France, US, UK, Netherlands, Italy, Germany) addressed key issues in the field, from research to industrialization, development, patient access and financing.

The GenoTher Summit 2025 also served as the official launch of the biocluster and was attended by approximately 350 researchers, investors, biotech executives and public decision-makers representing more than 100 organizations.

GenoTher is a catalyst for synergies. It brings together in a unique hub researchers, clinicians, GMP manufacturing capacity, pharma/biotech and industrial players, training resources, patient representatives, investors, and public decision-makers around a common ambition: to establish a leading gene therapy ecosystem, accelerate innovation, and deliver new genetic therapies for rare and common diseases through strong partnerships and a unified vision of therapeutic innovation.

Genethon CEO Frederic Revah, who serves as President of GenoTher, said, "The GenoTher Biocluster represents our ecosystem's leadership inshaping the international landscape for gene therapy as a priority for new drug development. Our co-founders and partners all have made significant advances in gene therapy. Together we have the capability of creating the next generation of gene medicine technologies for rare diseases and for therapeutic interventions for frequent disorders, including gene editing and RNA-based therapies, for a broad range of diseases."
Learn more about the summit.



Above: Dr. Frederic Revah, PhD, CEO of Genethon and President of GenoTher at the 2025 Summit Meeting.

RESEARCH COLLABORATIONS

High-Throughput Screening Identifies Two Compounds for Potential Treatment of Limb-Girdle Muscular Dystrophy (LGMD-R2)

Genethon, I-Stem and the Institute of Myology collaborated on work published in the British Journal of Pharmacology identifying a pharmacotherapy to treat LGMD-R2. The genetic disease is caused by mutations of the DYSF gene encoding dysferlin, a transmembrane protein essential for muscle cell membrane repair mechanisms. The loss of dysferlin function results in progressive weakness and wasting of proximal muscles.

The research began with development of a high-throughput in vitro screening test using immortalized myoblasts, which form muscle tissue. This test made it possible to select molecules from a library of 2,239 clinically approved drugs and bioactive compounds. The researchers identified two compounds, saracatinib and bazedoxifene, that increase dysfelin content in cells with the DYSF gene mutation.

The researchers concluded that saracatinib and bazedoxifene are potential treatments for LGMD-R2, and that the widespread protective effect of bazedoxifene reveals a new avenue toward genotype-independent treatment of LGMD-R2 patients. **Read More.**

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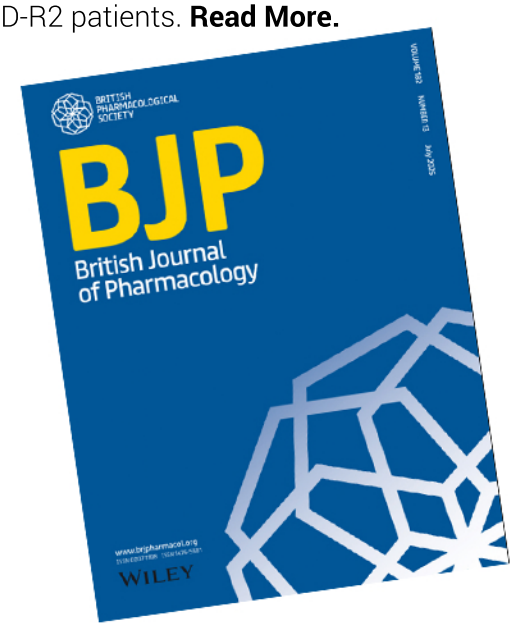


Patrick Santambien, PhD
Genethon Director of Technological Development

Genethon and Eukarys Enter Strategic Partnership to Develop a Breakthrough Technology to Reduce Gene Therapy Biomanufacturing Costs

Eukarys, a biotechnology company in Evry, France, has developed an engineered enzyme, C3P3, which significantly increases the production capacity of cells used for biopharmaceutical synthesis by enhancing their mRNA synthesis capabilities.

Combined with Genethon's expertise and technologies, this innovative approach could significantly improve the production of AAV (adeno-associated virus) vectors, used in gene therapy.

Patrick Santambien, Genethon's Director of Technological Development, said, "For more than fifteen years, Genethon has been pushing the boundaries of gene therapy biomanufacturing by focusing on innovative approaches. Eukarys' technology is truly disruptive to biomanufacturing in general and holds great promise for delivering gene therapy products based on AAV vectors under optimal conditions, while drastically reducing biomanufacturing costs. We are excited about this partnership, which could pave the way for much more affordable therapies." **Read more**

Mario Amendola
Head of the Genethon Gene Editing Laboratory

Genethon Contributes to Design of Innovative Vector for Use in Gene Therapy for Sickle Cell Disease

Genethon's Head of the Gene Editing Laboratory, Mario Amendola, collaborated with the Paris-based Institut Imagine's Annarita Miccio and Marina Cavazzana on the design of a lentiviral vector for use in gene therapy to treat sickle cell disease.

SK pharmteco Cell & Gene Europe (Yposkesi), AP-HP, Institut Imagine, and AFM-Telethon, founder of Genethon, are collaborating on production of the breakthrough vector technology for a clinical trial. The collaboration focuses on using an ex vivo hematopoietic stem and progenitor cell (HSPC) gene modification approach with the lentiviral vector.

The strategy consists of introducing a therapeutic gene into the patient's hematopoietic stem cells enabling the production of functional red blood cells. The major innovation is based on the introduction of microRNA, a dual strategy that both inserts a gene of interest and reduces the expression of the diseased gene.

Dr. Amendola, with his expertise in microRNAs developed through other projects, contributed to this breakthrough. His experience made it possible to optimize the construction of the lentiviral vector, thus promoting the expression of the therapeutic gene. **Read more.**

Genethon Receives Grant to Research Treatment for Myhre Syndrome

Myhre syndrome is a rare, genetic disorder caused by mutations in the SMAD4 gene that affect connective tissue. Children with the disease suffer from short stature, facial dysmorphism, joint stiffness, and potential cardiovascular and respiratory complications.

The Myhre Syndrome Foundation, based in Texas, awarded a $450,000 grant to fund a groundbreaking research project designed by Genethon in collaboration with Professor Valérie Cormier-Daire (Genomic Medicine Service for Rare Diseases, Necker-Enfants Malades Hospital) in France. There is no cure for Myhre Syndrome and the project aims to develop a potential treatment for the life-threatening complications of the disease. **Read more.**