NEWSLETTER

GENETHON
CURE THROUGH INNOVATION

2023 Issue Number 1

CEO COMMENTARY

IMPORTANT ACHIEVEMENTS, KEY CHALLENGES AHEAD

"Genethon made important achievements in 2022, but we still face key challenges in the year ahead."

In 2022, Genethon has achieved three major milestones in the clinical trials that we are sponsoring. First of all, our gene therapy trial for Duchenne muscular dystrophy resumed, following an exceptional partnership between sponsors of several gene therapy trials currently in progress for this disease. This partnership helped us understand the origin of the unwanted side effects observed both in our trial and in others. Since then, additional boys have been treated, and the trial continues to recruit.

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INSIDE

A first patient was treated in a European gene therapy trial for FKRP-related limb girdle muscular dystrophy. This signaled the culmination of 30 years of high-level research conducted in our laboratory by the team of Isabelle Richard, a world specialist in these pathologies. This trial is led by Atamyo Therapeutics, a spin-off of Genethon, which we created to speed up gene therapy development for limb girdle muscular dystrophies. We also aim to bring four other products for four other types of limb girdle muscular dystrophy to the clinical stage. An exceptional pipeline.

Lastly, the entry into pivotal phase of the trial for Crigler-Najjar syndrome is the result of the positive data obtained in the initial clinical trial among the first patients treated. We are delighted with this new step, which brings so much hope to patients affected by this serious liver disease.

A total of 13 of our gene therapy products stemming from our R&D have reached clinical trial throughout the world and 6 others should reach this phase in the coming three years.

Challenges ahead

Gene therapy has reached maturity, shows a strong dynamism, and the wide variety of trials and medications currently available - 24 in total for rare genetic diseases as well as for several forms of cancer - demonstrate that this innovative technology, which we have helped to develop, has become a distinct form of medicine.

Five new gene therapy products were approved in 2022 in the US or in Europe: Biomarin's Roctavian for Hemophilia A; UniQure's Hemgenix for Hemophilia B; PTC's Upstaza for AADC deficiency; Ferring's Adstiladrin for NMI Bladder Cancer; and Janssen's Carvytki CAR-T approach. 2023 could be even more productive with 11 new products being considered for registration, half of which for genetic diseases.

However the field, and by extension Genethon, face several crucial challenges in 2023.

The first concerns patients' access to these innovative medications, particularly in the field of rare diseases. The 7,000 known diseases affect 350 million people throughout the world, but individually they affect sometimes only a few hundred patients.

Although very many rare diseases could benefit from gene therapy treatment based on the treatment paradigm developed over the past few years, the rarity of some of these diseases and the high cost of both product development and production mean that pharma and biotech companies don't consider them "profitable" enough.

It is therefore vital to find a creative economic model and also to innovate in terms of bioproduction to reduce costs, control the price of medications sold and as a result secure access. To help meet this challenge, in addition to the daily efforts of its experts on these issues, Genethon has joined the Bespoke Gene Therapy Consortium, launched in October 2021 by the Foundation for the National Institutes of Health.

The second challenge involves immune response control. This immune response, in particular for AAV vectors, is a limitation on re-dosing of the product, which may be necessary for a patient already treated. Some patients (up to 30-40%) also have natural immunity against the vectors and are not eligible for treatments. Lastly, in some cases, the immune response to injected products may be the cause of side effects.

We need to design innovative strategies to control and bypass these immune responses. Genethon is working on this, with promising research taking place in one of our teams to overcome this hurdle. We hope to be at the forefront of innovation for this second generation of gene therapies as we were for the first generation at the end of the 1990s.

PRODUCT DEVELOPMENT

Clinical Trial Launch and Interim Trial Results

Limb-Girdle Muscular Dystrophy

A European Phase1/2 trial of a replacement gene therapy (ATA-100) for FRKP-related limb-girdle muscular dystrophy (LGMD2I/R9) is under way in Denmark, France and the U.K, sponsored by Atamyo Therapeutics.

"This is an exciting milestone for our company but most importantly, if this clinical trial is successful, it could have a life-changing impact for patients affected by LGMD-R9," said Stephane Degove, Chief Executive Officer and Co-Founder of Atamyo Therapeutics.

A spin-off of gene therapy pioneer Genethon, Atamyo leverages unique expertise in AAV-based gene therapy and muscular dystrophies from the Progressive Muscular Dystrophies Laboratory at Genethon.

Read the Atamyo Press Release for more details

Crigler-Najjar Syndrome

Genethon has launched a pivotal clinical trial in Europe for treatment of Crigler-Najjar syndrome, a life threatening liver disease. The trial of the gene therapy, GNT-0003, which combines normal copies of the UGT1A1 gene coding for the bilirubin metabolizing enzyme with an AAV vector, will be conducted in France, Italy and the Netherlands and will enroll patients aged 10 years and older with the objective of confirming efficacy and safety seen in the previous clinical trial.
Read the press release for more details.

Harnessing the Liver as a Biofactory

"Our research demonstrates that AAV gene therapy can harness the liver as a biofactory to express soluble factors capable to act on distant organs. This approach, here used to correct Crigler-Najjar syndrome, can potentially be applied also to other rare life-threatening, inherited diseases," said Giuseppe Ronzitti, Head of the Immunology and liver gene transfer team at Genethon. "Our results also support the use of the liver as a platform to secrete factors able to modulate pathways in tissues refractory to AAV gene therapy, such as bone or kidney, further expanding the therapeutic potential of the approach."
Read here for more details.

Wiskott-Aldrich Syndrome

Genethon announced in Nature Medicine that its lentiviral based gene therapy, developed in collaboration with French and British teams, has demonstrated long-term efficacy in eight patients with Wiskott-Aldrich syndrome, a rare and severe immune deficiency

Read for more details.

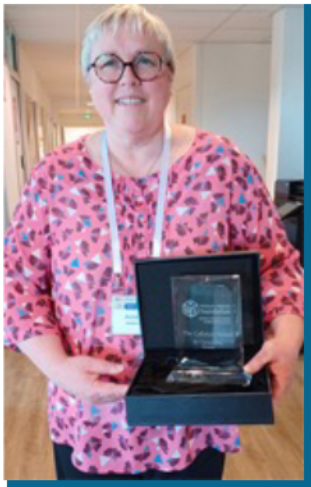
SCIENTIFIC PUBLICATIONS

Muscular Dystrophy Research

Genethon helps clarify a molecular mechanism of mitochondrial malfunction in Duchenne muscular dystrophy.

Results of a study were published in *Life Science Alliance (Dlk1-Dio3 cluster miRNAs regulate mitochondrial functions in the dystrophic muscle in Duchenne muscular dystrophy | Life Science Alliance (life-science-alliance.org)* demonstrated that in the DMD muscle, the upregulation of a microRNA (miR-379), represses the expression of mitochondrial proteins and ATP production. This reduction in energy production can accelerate the damage which is caused by the disruption of calcium homeostasis in the mitochondria of the dystrophic muscle.

Read more about this research



AWARDS

Genethon's Anne Galy Awarded Callahan Prize by WAS Foundation

The Wiskott-Aldrich Syndrome (WAS) Foundation has awarded the Callahan Prize rewards Genethon's success in developing a gene therapy for this rare genetic disease, "**This award is great recognition of the work accomplished and I was very touched to receive it from the hands of Dr. Sumathi Iyengar, who has worked so hard to advance research and make treatments available to patients,"** rejoices Anne Galy, Inserm research director and head of Genethon's Immunology and biotherapies team who has worked for more than 20 years on Wiskott-Aldrich syndrome, a severe immune deficiency of genetic origin.
Read more

RESEARCH

Collaborations

Sickle-cell Anemia: a project involving the gene editing team has just secured European funding.

The "EDITSCD" project which aims to improve gene editing strategies for sickle-cell anemia, a hereditary disease of the red blood cells, has just been selected by the European Union. It will involve a dozen or so research laboratories in Europe, among then the Gene editing team headed by Mario Amendola at Genethon.

Read more

Genethon joins Bespoke Gene Therapy Consortium launched in October 2021 by the Foundation for the National Institutes of Health (FNIH) as part of its Accelerating Medicines Partnership® (AMP®) program.

The consortium is a public-private partnership bringing together the resources of the U.S. National Institutes of Health (NIH) and Food and Drug Administration (FDA) with biopharmaceutical companies and other non-profit groups. The goal is to speed development of customized (or bespoke) gene therapies for millions of people worldwide suffering from ultra-rare diseases.

Read the Press Release for more details.

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