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If this pace continues, the next five years could bring more progress than the last fifteen.

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Genethon sits at the forefront of a fast-accelerating moment in gene medicine, where decades of foundational research are now translating into clinical progress across rare liver, neuromuscular, immune and ophthalmic diseases. In this interview, FrÃ©dÃ©ric Revah reflects on the organisationâ??s scientific evolution, its approach to partnerships and access, and the emergence of GenoTher as Franceâ??s coordinated engine for next-generation therapies. The exchange offers a clear view of how a patient-founded laboratory is helping reshape the trajectory of gene therapy in Europe.

What is Genethon, and how has its mission evolved since its creation?

Genethon was created in 1990 by AFM-TÃ©lÃ©thon as a non-profit research organisation dedicated to rare genetic diseases. Founded by families affected by neuromuscular and genetic conditions, we have always operated with a patient-centred purpose. In our early years, we contributed to the deciphering of the human genome and produced the first high-resolution maps between 1992 and 1996, a contribution that placed us at the forefront of international genome research.

By the late nineties, we redirected our focus toward gene therapy at a moment when the field was still viewed as uncertain and technically demanding. Long-term support from AFM-TÃ©lÃ©thon allowed us to invest in approaches that few others were willing to pursue. Approximately three-quarters of our funding since inception has come through TÃ©lÃ©thon donations, which have

provided the continuity needed to build deep expertise over time. Today, we resemble a mid-sized biotech with around 220 to 250 employees, yet we remain a mission-driven nonprofit organisation focused exclusively on rare genetic diseases.

Over the years, we built capabilities across the entire gene therapy continuum. This covers vector design, preclinical and translational evaluation, and a very early commitment to manufacturing. We understood that access to clinical-grade vectors would be a decisive factor in taking programmes to the clinic and invested heavily in bioprocess development for these complex modalities. By 2006, we launched one of Europeâ??s first human gene therapy trials for a rare muscle disease. Today, around fifteen clinical programmes originate from our work across diseases of the immune system, the blood, the liver, the eye and neuromuscular disorders. One of the clearest demonstrations of long-term impact is spinal muscular atrophy (SMA), where Zolgensma, now marketed by Novartis, builds on proprietary technology and preclinical research developed by our teams in the mid-2000s.

Alongside the clinical work, we continue to advance enabling technologies. We design next genÂ-eration viral vectors, including engineered capsids that improve muscle targeting and reduce liver exposure, and we recently published artificial intelligence-driven research that led to LICA1, a new capsid with an enhanced profile for muscle therapies. We are also working to reduce the cost of vector production through a combination of incremental improvements and more disruptive approaches, such as a plant-based AAV system developed with Samabriva. More broadly, we continue to explore solutions to long-standing challenges in gene therapy, including immune responses to viral vectors and the need for more scalable and accessible manufacturing models.

How would you characterise the scope of Genethonâ??s current clinical pipeline and the scientific capabilities that sustain it?

Our pipeline reflects more than two decades of sustained work in gene therapy and now includes around fifteen clinical programmes derived from our research. These programmes span diseases of the immune system, the blood, the liver, the eye and the neuromuscular domain, supported throughout by our platforms in vector engineering, non-clinical evaluation, translational science and manufacturing.

In ophthalmology, the Phase three programme for Leber Hereditary Optic Neuropathy (LHON), now led by GenSight, illustrates how we operate. Foundational research at the Institut de la Vision received early support from AFM-TÃ©lÃ©thon, after which we delivered the preclinical studies, safety package and initial clinical-grade vector batches before transferring the programme for full development. This model, where we build the bridge from academic science to clinical translation, remains a core part of our mission.

In liver diseases, we are advancing GNT0003 for Crigler-Najjar syndrome, which has now entered the pivotal phase in Europe with encouraging signs of efficacy and safety. To overcome one of the major barriers in gene therapy, namely pre-existing immunity to AAV vectors, we launched the GNT-018-IDES study. The first patient enrolled carried anti-AAV8 antibodies yet was able to receive GNT0003 after an imlifidase pre-treatment that transiently removed these antibodies. This represents a meaningful step forward, as a substantial proportion of patients worldwide present with natural AAV immunity and would otherwise be excluded from treatment opportunities.

Our most advanced neuromuscular programme is GNT0004 for Duchenne muscular dystrophy. DMD results from mutations in the dystrophin gene, which is too large to be packaged into an AAV vector. We designed a micro-dystrophin construct that retains the essential functional regions of the full protein and developed it with Professor George Dicksonâ??s group in the United Kingdom and

the Institute of Myology in Paris. Early data in boys aged six to ten show microdystrophin expression, sustained reductions in creatine kinase, and stabilisation of motor function relative to untreated patients followed in parallel. These outcomes, observed consistently across the treated cohort, allowed us to enter the pivotal Phase three trial in Europe and the United Kingdom. The programme uses a markedly lower dose than many other AAV-based approaches, which has implications for both feasibility and safety. We are now seeking a partner who can support late-stage development and future access.

Beyond Duchenne, we contribute to research in amyotrophic lateral sclerosis (ALS) through the European MIROCALS study, where we provide DNA bank and sample support for the low-dose IL-2 strategy. In parallel, we are exploring early gene therapy concepts for ALS with a translational team at the Institute of Myology in Paris. These remain preclinical but expand the horizon of what we may be able to bring forward.

How do you approach partnerships and access as your programmes move toward late-stage development?

Our strategy reflects the diversity of the diseases we work on and the realities of bringing a gene therapy to patients affected with rare diseases. In areas where a viable commercial pathway exists, partnering with an established industry player can be the most effective route to broad access. The SMA programme illustrates this well. We licensed our AAV9-SMN1 intellectual property to AveXis in 2018, and following its acquisition by Novartis, the therapy reached global scale. It shows how early research and intellectual property generated at Genethon can enable downstream industrialisation when aligned with the right partner.

For DMD, we take a similar view. A large-scale partner can support access and share the financial weight of a Phase three trial. Yet much of our work concerns ultra-rare conditions where only a handful of patients are diagnosed each year across Europe. In these cases, there is no sustainable commercial model, and we often have more promising programmes ready for clinical evaluation than we are able to finance. This is a structural limitation faced by any organisation working in this field.

To move these therapies forward, we need to address the factors that drive cost. Manufacturing remains a major contributor, so we continue to refine production processes and develop more powerful vectors that require lower doses. Regulatory requirements also play a role. Current frameworks often mirror those used for large population diseases, even when the indication is extremely rare. We believe a more proportionate approach is needed, one that preserves patient safety while applying requirements in a way that reflects the scale of the disease.

Financing the clinical stage is equally important. When a programme reaches trials, it carries real meaning for families, and we receive messages from across the world from parents asking whether their child can participate. In Europe, approved treatments are reimbursed, yet there is little public support for the clinical development of therapies for ultra-rare diseases. The recent story highlighted in the New York Times, where a child lost access to a promising treatment when funding stopped, shows how fragile the current model can be. For these reasons, we see partnerships, adapted regulatory pathways and dedicated public support as essential if we want gene therapies to reach patients with the rarest conditions.

How do you decide which programmes to prioritise for clinical advancement, and what role do collaborations play in that process?

We make deliberate choices about which programmes enter the clinic because we cannot advance all of them. Our decisions hinge on two considerations. We prioritise candidates with the strongest potential to deliver meaningful benefit for patients, and we move forward with those for whom we can secure a realistic development path. Even with the ongoing Phase three in Duchenne, the constraints are clear. Not every programme can progress at the same pace, and we focus our resources where the scientific promise and the feasibility of financing align.

Partnerships have become essential to this approach. Over the years, we have developed several models that allow us to adapt to the needs of each project. Some programmes are pursued through co-development, where we share responsibilities and jointly navigate the translational and clinical stages. Others follow a handover model in which we provide the technology, preclinical and non-clinical foundations and initial manufacturing, after which a partner leads full development. We also collaborate with academic groups that have strong science but lack the infrastructure to reach first in human studies. In these cases, we help shape the programme, deliver the regulatory package and produce the first clinical-grade batches.

This flexibility allows us to progress more therapies than we could on our own. It creates practical pathways for innovation developed in our laboratories to reach clinical testing and, ultimately, patients living with rare genetic diseases.

How do you view Franceâ??s position in gene therapy, and which factors are shaping its competitiveness in this field?

France holds a distinctive position in gene therapy, grounded in a long track record of scientific achievement and supported by an ecosystem that spans fundamental research, clinical translation and industrial scale biomanufacturing. The early success at HÃ´pital Necker-Enfants Malades for children with X-linked severe combined immunodeficiency, led by Alain Fischer and Marina Cavazzana Calvo, remains a defining milestone in modern gene medicine and helped establish the clinical expertise that continues to anchor the field in France. The patient association AFM-Telethon has played an instrumental role by massively supporting, across the board, gene therapy initiatives from upstream discovery to clinical trials. The country has built a coherent environment for advanced therapies, with leading centres capable of running complex trials and facilities such as Yposkesi, which now operate among the largest viral vector production sites in Europe.

This scientific base is strengthened by a clear national strategy. Through the France 2030 programme, the government designated five bioclusters as strategic engines for health innovation, including GenoTher, which focuses specifically on gene and cell therapy technologies. GenoTher has received a public funding envelope of seventy million euros over five years, supplemented by private commitments that bring the total to roughly one hundred and forty million. Its mission is to provide shared manufacturing and vector platforms, clinical design support, access to clinical investigation centres, patient data capabilities, training programmes and structured access to international investors. Few countries have an initiative of comparable scale, and it reflects a deliberate effort to secure a leadership position in gene medicine.

The regulatory environment also plays an important role. The ANSM and the European authorities provide a stable and pragmatic framework for advanced therapies, and several gene therapy products have been authorised in Europe before receiving clearance in the United States. At a time when other regions are experiencing greater regulatory uncertainty or fluctuations in R&D investment, this predictability has become a competitive advantage. It is visible in the growing interest of international experts who now approach Genethon to explore opportunities in France.

Taken together, these elements create a favourable setting for gene therapy research and development. The combination of scientific depth, clinical expertise, manufacturing capacity and national commitment positions France as one of the most attractive environments in Europe for teams working at the frontier of gene medicine.

How is GenoTher progressing, and what direction do you expect it to take as it scales?

GenoTher entered its operational phase with the first GenoTher Summit in June 2025 in Ã?vry, which followed its official accreditation the previous year. The meeting brought together more than twenty international experts and more than three hundred and fifty participants from research, industry and investment, and opened with the first session of our Scientific Advisory Board. The calibre of the contributors confirmed the momentum building around the cluster.

The ambition now is to create an integrated engine for gene therapy innovation, training and manufacturing within one coordinated framework. GenoTher brings together partners with strong scientific visibility and assembles the full set of platforms required for advanced therapies, from viral and non-viral vectors to gene editing, organoid systems and next-generation bioprocess technologies. These capabilities are designed to support both established teams and early-stage innovators.

The cluster is anchored by major French institutions. AP-HP and Institut Imagine provide a complete translational environment that links basic discovery, clinical investigation and patient care. Genethon acts as a founding pillar alongside partners such as Spark Therapeutics, Nava Therapeutics, with several universities and academic groups adding further depth. The ecosystem also includes a strong investor network, patient associations and local communities, which strengthen the support structure available to emerging projects.

A key dimension of GenoTher is the development of new entrepreneurial talent in gene medicine. We have introduced a structured sourcing and selection process through an investment committee and offer incubation, access to shared technologies, mentoring and early financing. These elements position GenoTher as a coordinated national resource capable of accelerating the next wave of gene therapy programmes and reinforcing Franceâ??s role as a leading centre for advanced therapeutic innovation.

What progress do you expect over the next few years, and what would you hope to have achieved by then?

I feel a strong sense of optimism about the trajectory of gene therapy. The recent ESGCT congress made clear how quickly the field is advancing and how the scope of what we can treat is expanding. We are moving beyond the early period of ultra-rare, single-patient interventions that first proved what was technically possible, and we are beginning to see credible progress in larger rare diseases. The first encouraging signals in Huntingtonâ??s disease are a good example. Although these data do not come from us, they matter because Huntingtonâ??s has resisted meaningful advances for decades. Similar momentum is emerging in age-related macular degeneration (AMD) and Parkinsonâ??s disease.

Oncology is also entering a new phase. CAR-T therapies continue to evolve, with work extending beyond haematologic cancers into solid tumours, and the field is gradually shifting from ex vivo to in vivo approaches. If this pace continues, the progress achieved over the next five years could exceed what we have seen in the past fifteen. That is the direction I expect, and the direction I hope the field

will be able to point to when assessing the impact of this period.

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