FrÃ©dÃ©ric Revah â?? CEO, Genethon; President, YposKesi, France

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Genethon, a laboratory created by the patient organization AFM-Telethon, is one of the worldâ??s leaders in the development of biotherapies for rare diseases. In this interview Genethonâ??s CEO FrÃ©dÃ©ric Revah explains its role in the discovery of innovative therapies since the 1990s and the recent launch of YposKesi, its innovative (and profitable) manufacturing platform.

Could you introduce Genethon to our international audience?

The creation dates back to 1990, when AFM-Telethon decided to create an institute for the development of therapies for rare genetic diseases. Today, in a time when the field of gene therapy is experiencing an exponential growth, Genethon is probably a pioneer, as it is one of the oldest organization completely focused on this field in the world. We started in 1996-1997, when the industrial interest in gene therapy was decreasing. Indeed, at the beginning of the 1990s, there had been some interest in gene therapy, as it was seen as a possible way to treat any disorder, including frequent and non-genetic ones. Soon, it became clear that the field would not deliver such results, and the industrial players withdrew. However, the Association FranÃ§aise contre les Myopathies AFM-Telethon (the French Muscular Dystrophy Association) firmly believed that gene therapy could be a game changer in rare genetic disease, and, through Genethon, it heavily invested in the field.

To put this into context, in that period, France was leading the research in gene therapy. In 1999, Prof. Alain Fischer performed the first successful trial at the HÃ´pital Necker, demonstrating the possibility to treat immune-deficient babies by gene therapy, transferring corrective genes in their immune system cells. In this way, the immune functions were restored, and the treated children, who had originally an expected life-span of 3-4 years constrained in a completely sterile bubble, were able to live and grow.

What has been the evolution of Genethon since its creation, and how would you describe your main achievements?

In the 1990s, the human genome had not been deciphered yet. The first step after the foundation of the organization was to participate in the global effort. The first high resolution map of a genome was finally reproduced at Genethon between 1992 and 1996, by the team led by Jean Weissenbach and Daniel Cohen. Though it was just the first step, it was a critical move for a faster identification process of the genes responsible for genetic diseases.

Following this incredible and early success, Genethon focused on therapy. Indeed, our objective was not to be a genetic institute, but rather to develop the tools and the know-how for the design, testing and manufacturing of gene therapy programs. After 10 years of learning, we started manufacturing in 2006. Biomanufacturing was a critical step to develop clinical trials. We upgraded our small twenty-person facility to one of 5000 sqm in 2013, and it was at that time the largest gene therapy manufacturing facility in the world.

After this milestone, Genethon started developing products for rare diseases in different therapeutic areas, such as immune, blood, neuromuscular, liver and retinal disorders. Right now, we have eight products in clinical trials: some of them have been completely developed in-house, others through external collaborations. Let me give some examples of our successes. Genethon discovered and patented a gene-therapy product for spinal-muscular atrophy the product was licensed and developed by AveXis, now owned by Norvartis, and they are still operating under a license from Genethon. Similarly, the leading product of Audentes Therapeutics, a West Coast company listed on the NASDAQ, was developed here up to the animal testing phase. Clinical trials started one year ago and we are witnessing spectacular results. We have outlicensed a product to Orchard Therapeutics, and we are co-developing a Duchenne dystrophy program with Sarepta, a US biopharma listed on the NASDAQ. The list of licensed products is long. Similarly, in other cases, we have continued development in-house through international trials.

Genethon has quite a unique model. What is the effect of such a model on your research?

Our founder is a patient organization, making us a unique case. You could see us as the laboratory of a patient organization, as a biotech company, a portfolio of licensed or internally-developed compounds, and a nonprofit, all at once! Contrary to the common perceptions of nonprofits, there is a economical value to our activities: today around 60% of our funding comes from AFM-Telethon but we are steadily increasing the portion that is derived from licensing revenues.

Nevertheless, we would never have achieved what we did in the field of genetics if we were a regular for-profit company. Back in the 1990s, no investor would have invested for that long in a field considered as dead, and up to 2011, no pharmaceutical company would have put a dime into gene therapy. So, it is safe to say that the nonprofit status is a fundamental aspect.

You have been at the helm of the organization for eight years. What would you like Genethon to become in the next eight years?

I want Genethon to be the leader in two aspects. The first is the design and technical evaluation of gene therapy, in particular for neuromuscular diseases. To achieve this objective, it is important to adopt a multifaceted approach by working with the best muscle physiologists, the best clinicians, and the best scientists. We need to reach new heights in clinical evaluation, pre-clinical science and physiology. We need to understand the expectations of the patients, the molecular and cellular mechanisms that we want to target with our products and the appropriate predictive models for degenerative diseases.

The second point, and this is what makes gene therapy unique, is manufacturing. Its cost is spectacular, in particular for neuromuscular diseases. Today, the production of a single dose for the treatment of a Duchenne muscular dystrophy needs a 200-liter bioreactor, which would be enough to produce thousands of doses of other type of products such as vaccines. The methods, the technologies, and the processes need to be significantly improved. On one side, there is the

opportunity for incremental advancement, aimed at gaining a few percentage points. On the other, there is space for game-changing improvements that would reduce costs by a factor 20, or even a 50. Gene therapy has a unique feature: a very large part of the final value derives from manufacturing. This aspect is so vital that at Genethon we have a whole team dedicated to innovations for manufacturing. In particular, having YposKesi [an expert industrial platform exclusively dedicated to gmp manufacturing and development of gene and cell therapy products. The company was founded by AFM-Telethon in 2016 together with BPI-France to cover the needs of Genethon lab and serve as a CDMO for third parties. It is across the street and this is very important in this aspect.

In the same way France has been a pioneer in gene therapy, do you think that it has the potential to become one of the first nations to innovate the manufacturing process?

This is at stake. If we are not able to innovate in manufacturing, the products invented in France will have to be produced elsewhere. It would be an incredible loss in economic value for our country. Of course, we are not trying to do this all by ourselves; we are trying to get the support of the authorities and the involvement of industrial players.

What do you think are the strengths of France in gene therapy?

The strength lies in the fact that there is a strong expertise on the scientific and the clinical side of things. What we are missing and what we are trying to bring to the table with YposKesi is the industrial element attached to it. Ideally, YposKesi will be the new nucleus allowing the crystallization of knowledge in the value chain. Certainly, an issue in the French and European markets is the lack of funds. A lot of our products have been licensed to US companies, just because they have the money or they are in the position to raise substantial funds. If we want to keep these products in Europe we have to find ways to raise funds here.

What is the raison dâ??Ãªtre of YposKesi and your vision for it?

Genethon has been involved in bioproduction since 2006 and then opened a large manufacturing facility in 2013. At that time, manufacturing was an integrated part of Genethon, funded by public generosity and not for profit. However, we started thinking that to grow we had to create a separate entity. We convinced the French public investment bank (BPI France) to invest in the foundation of a new company, YposKesi, completely dedicated to the manufacturing and selling of gene therapy. YposKesi is a complicated name but it has a meaning in Greek: promise.

The company was founded recently, in 2016, in a period where paths of production for gene therapy are strongly evolving in Europe and the US. Nevertheless, YposKesi has a unique strength â?? the strong connection with Genethon and its innovative power, as well as 20 years of expertise. The idea is not only to be manufacturers and have Genethon as a client. We work with big pharma and biotech, bringing to the table the most advanced technology for gene therapy manufacturing and helping them improve their processes. In a nutshell, it is a production platform that acts as a service organization. Today we have 5,000 sqm, four production suites, and a manufacturing capacity of 35 batches a year using multiple technologies. We are planning on expanding to a second building that should be operational in 2021, doubling the capacity.

As YposKesi we would like to see the industrial field of gene therapy grow. We already see the French public investment having a very wise and visionary pattern. Of course, there is a risk attached to it, as we see the increasing rate of products under registration, but there is still a very high economic value. There is a general opinion that France has, to some extent, missed the train for the manufacturing of monoclonal antibodies and recombining proteins. The idea is that we want to be sure that France stays at the forefront and to translate its 2000â??s leadership from the clinical side to an industrial position.

Philippe Lamoureux, the Director General of LEEM (the industry association for the French pharma companies) explained the need to train and recruit the workforce to a â??new pharma,â?? one that is less concerned with the traditional chemistry foundation.

Yes, I agree. We also have to somehow ensure that sufficient attention is given to the industrial side of things. There has been the tendency to undervalue the industry, with the idea that most of the value is more related to the design and the research side of things. This is not true for biotherapeutics. Not focusing on the manufacturing capability entails the risk of shortages.

YposKesi was the only private company mentioned in PM Edouard Philippeâ??s speech delivered during the Strategic Council for Health Industries (CSIS). What are your feelings about this 8th editon of the CSIS?

I think there is a unique opportunity right now in France for pharmaceutical companies. Although Genethon is atypical in the pharma environment, we were the first nonprofit organization to receive the Prix Gallien France, awarded to the company offering the best therapeutic innovations available to the public.

All the stars are aligned for France right now: we have a government aiming at healthcare innovation, a network of top-notch scientists and physicians, unique initiatives, and innovations in gene therapy that we would have never dreamt of. In 1999, when Dr. Fischer did his clinical trial, we never thought it would be applicable to other rare diseases. The field is ready for future growth, as was apparent in the CSIS during which â?? as you mentioned â?? YpoSkesi was the only company mentioned by the Prime Minister.

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