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Developing gene and cell therapies for rare diseases: an opportunity for synergy between academia and industry

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ABSTRACT

For the last twenty years, academic research has been the major, and often only, driving force behind the spectacular development of gene transfer technology for the therapy of rare genetic diseases. Investors and industry became eventually interested in gene and cell therapy, due to the success of a series of pioneering clinical trials that proved efficacy and safety of last-generation technology, and to favorable orphan drug legislation in both Europe and the United States. Developing this forms of therapy is however complex and requires skills and knowledge not necessary available to the industry, which is better placed to develop processes and products and put them on the market. Cooperation between academia and industry is an opportunity to de-risk innovative approaches and ensure a faster and more economical development of therapies for diseases with high unmet medical needs and low profit expectations.

Twenty-five years ago, bone marrow cells genetically corrected with a retroviral vector were administered to a child suffering from adenosine deaminase-deficient severe combined immunodeficiency (ADA-SCID), a rare disorder of the immune system. This was the first attempt to use genetically modified stem cells to treat a human disease.[1] The publication of this study, and of a parallel one that used peripheral blood T cells to treat the same disease, marked the beginning of clinical gene therapy.[2, 3] On May 26, 2016, GlaxoSmithKline (GSK) announced that the European Medicines Agency had granted marketing authorization to Strimvelis®, the commercial name of gene therapy for ADA-SCID.[4] It took over 20 years of clinical investigation, technological improvements and a landmark clinical trial to prove the efficacy and safety of this therapy, and grant it market access.[2, 5-8] During the same period, *ex vivo* as well as *in vivo* forms of gene therapy for genetic diseases were developed and tested in a rollercoaster of successes, failures and severe adverse events that showed that integration of viral elements in the human genome can have consequences[9] and that our immune system is a formidable obstacle for any foreign intruder[10]. More recently, a series of authoritative clinical studies proved that gene therapy can change the course of many genetic diseases, from immunodeficiencies to retinal degenerations, lysosomal storage disorders, hemoglobinopathies and hemophilia (reviewed in Naldini 2015[11]). Some of these treatments will access market in the next two to five years, contributing to give to gene therapy its definitive place in clinical medicine. Why did it take so long, and who were the actors in this long and difficult process?

The regulatory and financial context of gene therapy

Designing, developing and manufacturing gene therapy products is a complex process, so far ventured essentially by academic research and clinical centers. Legislation introduced a decade ago in Europe and the US demands that these products are produced under the same good manufacturing practices (GMP) developed for chemical drugs, in pharmaceutical establishments built and operated with industry-like standards and licensed by governmental agencies. The regulation applies also to the even more complex combination of viruses and patients' cells at the basis of gene therapies such as that for ADA-SCID, which may be viewed as engineered autologous transplants, a personalized medicine by definition, rather than pharmaceutical "products". This regulatory framework is a formidable challenge for academic centers, which have been the only actors in the development of gene therapy until

very recently. These centers lack the human, financial and often cultural resources necessary for developing pharmaceutical products all the way through marketing authorization. This is traditionally the job of the pharmaceutical industry, perfectly equipped to understand and face the regulatory, manufacturing and marketing challenges of pharmaceutical development. For many years, however, the pharma industry stayed away from gene therapy, perceived as a dangerous technology of dubious efficacy, complex to develop, and addressing too small markets. This perception is changing rapidly: investors and industry now recognize that rare diseases and orphan drugs provide attractive niche opportunities and access to technology that might eventually prove useful for larger markets, such as neurodegenerative diseases or cancer.[12] The history of immunotherapy of cancer by autologous CAR-T cells is proving that the very concept originally developed to treat ADA-SCID, engineering a T cell by a retroviral vector, can now be used to treat refractory leukemia.[13] Hematopoietic malignancies are a much more interesting therapeutic target than a rare disease, even for large pharma, and this will likely foster industrial investment aimed at resolving the manufacturing and logistic challenges underlying the delivery of a complex, individualized cell and gene therapy treatment to thousands of patients.

A flourishing biotechnology industry is now aggressively licensing all the promising gene and cell therapies developed by academic centers in Europe and the US. However, taking over products the efficacy and safety of which has been provided by investigator-sponsored trials has proven difficult and expensive. As a matter of fact, most clinical trials, even the most successful ones, have been carried out with insufficiently developed products, produced with processes lacking the robustness, reproducibility and scalability requirements of a marketable product, and with insufficient analytical support. Completing their development very often implies re-developing the manufacturing process and proving an equivalent or superior efficacy in longer and riskier pivotal trials. The history of Strimvelis®, Glybera®, an AAV vector targeting lipoprotein lipase deficiency,[14] and Holoclar®, a limbal stem cell-based product aimed at replacing damaged corneas,[15] shows that a very long clinical development carried out essentially by academic forces is difficult to translate into a commercial product. Nevertheless, it has been done and it will be done again; can we envision a better way of having academia and industry cooperating towards a faster, less risky and more economical development of new therapies?

The benefits of academia-industry cooperation

An example of how academia and industry may cooperate is the alliance between the GSK giant and the charity-funded Telethon Institute of Gene Therapy (TIGET) in Italy. Under the alliance, GSK gained an exclusive license to develop and commercialize the pioneering ADA-SCID treatment, and an option to technology developed by TIGET to treat six more genetic diseases.[16] The scheme guarantees that new therapies are conceived and tested in a creative and flexible academic environment and eventually developed and marketed by professional with appropriate resources. Supervision from an industrial player already in the earlier phases of product and clinical development avoids errors in designing clinical studies, manufacturing processes and analytical tests, streamlines and optimizes the regulatory process, and reduces development costs. Furthermore, such a process fosters cross-fertilization and cultural exchanges that eventually benefit both the academia and the industrial partner. The positive results emerging from clinical trials of gene therapy for Wiskott-Aldrich syndrome[17, 18] and metachromatic leukodystrophy[19], two of the indications originally optioned by GSK, may soon prove the concept that academia-industry collaboration can develop complex gene therapy for rare diseases from concept to market in less than ten years.

A second example is the more classical, license-based partnership between Genethon, a French non-profit R&D organization funded by the AFM-Telethon charity, and Audentes Therapeutics, a biotechnology company based in San Francisco (CA)[20]. In the years 2010-2015 Genethon developed a gene therapy for myotubular myopathy, a lethal and very rare muscular disease due to deficiency of the MTM1 lipid phosphatase. The therapy is based on a single, systemic administration of an AAV vector, and proved its efficacy in pre-clinical studies in small and large animal models performed in collaboration with the University of Washington in Seattle.[21] Audentes licensed the therapy at an early pre-clinical phase, and the two organizations collaborated in designing the clinical development, developing a mid-scale manufacturing process, and going through the regulatory process necessary to authorize a single-phase trial in the US and three European countries. Again, the academia-industry collaboration created the synergy necessary to conduct what will be a pioneering attempt to develop a single treatment for a severe neuromuscular disease, with the highest scientific and professional standards and maximizing the chances of clinical and commercial success. This alliance reflects the different approach of the biotechnology industry, which prefers to

conduct a clinical trial in autonomy rather than waiting for the academia to provide the clinical proof of principle, as in the case of the TIGET-GSK alliance. The two approaches have pros and cons, but overall, both lower the cost and de-risk the investment in diseases with a tiny market, and both give the industry access to technology expandable to more profitable applications that can fully repay that investment, and eventually feedback on other rare diseases.

A serious, and yet underestimated limiting factor in the development of gene therapy is manufacturing of vectors and genetically modified cells. In both cases, the technology did not significantly evolve from that used in the first pioneering clinical trials, and is still based on cumbersome, labor-intensive, expensive and relatively small-scale processes. The academia that developed the ground-breaking transfection-based production systems for retroviral and AAV vectors, or the *ex-vivo* stem cell manipulation technology, is ill-positioned to evolve those basic concepts into robust, large-scale industrial processes that could reduce manufacturing costs and allow true commercialization of products. An emerging contract manufacturing industry is currently limiting itself to adapting processes transferred by clients, with little or no innovation and a still very limited production capacity. Serious industrialization can only come from the middle- to large-size biotechnology and pharma industry, the only players that can afford the significant investment required to develop commercial manufacturing technology.

Academia-industry collaboration has a potential impact also on the recently emerged issue of pricing advanced therapies for rare diseases. The expectations of the industry, particularly the small and medium size biotech, is of profitable prizes that allow to recover the investment and remunerate the investors, taking into account the small market size, the cost and complexity of manufacturing and delivering the products, and their uncertain life span in a scenario of rapidly evolving technology. The premium prices proposed for the first approved gene and cell therapy products raise concerns worldwide, particularly as for the long-term sustainability of such prices for the public and private payers in Europe and the US.[22] By de-risking and reducing the investment in the early development phases, the efforts of academia and charities may theoretically impact also on the pricing process. However, recognition of this impact is all but automatic, as price negotiation occurs very late in the process and is carried out only by sponsors and payers. The public investment, even when

considerable in size, could be forgotten, or not appropriately recognized, at the time of pricing. Charitable funding and patients' organization should use their access to governments and public opinion to have that investment fairly recognized, and make sure that prices do not become factors limiting patients' access to therapies, at least in some situations or countries.

What to do with diseases that will remain orphan of industrial interests?

Despite the positive role of academic research, many rare indications will still not attract industrial interest, for a variety of reasons. How do we make sure that scientists will continue to develop advanced therapies for rare diseases anyway? Should they all turn to the so-called hospital exemption legislation, which permits experimental therapies to be manufactured and used under the responsibility of a physician with limited regulatory supervision? If used responsibly, hospital exception permits to treat patients with therapeutics for which a GMP-compliant manufacturing process is unavailable, or treat patients outside the framework of a classical clinical trial to provide early proof of concept. Hospital exception should not, however, become a parallel investigation pathway, used by investigators just because the classical one is too difficult or too expensive. As stakeholders, governments, funding agencies, scientists and patient's associations should work on a model that facilitates the clinical development of really orphan gene and cell therapy products while maintaining high scientific, ethical and safety standards. There are many ways of doing so, like providing public subsidy to industrial subjects willing to take the risk of manufacturing and marketing such products, with a reasonable perspective of return on investment – the vaccine industry provides an obvious example. The European Union is about to revise advanced therapy legislation after a long trial period. It could redefine "products" and look again at the pathway to market. The complex combination of viruses and patients' cells at the basis of gene therapies like that for ADA-SCID are individualized treatments somewhere in between biotherapeutics and transplantable organs, which hardly meet the definition of "medicinal product" and should arguably be regulated differently. In addition, regulators are currently asking for an unreasonable amount of pre-clinical data and post-treatment monitoring in order to authorize a gene therapy treatment, even when pre-clinical models are uninformative and life-long monitoring too demanding and hardly enforceable for both academic and industrial players. A correct risk/benefit evaluation should be the major criterion for authorizing an experimental treatment. Applying a different standard to the advanced medicinal products is

unfair, discourages its development, and ultimately affects the right of patients to have access to cures in due time.

CONFLICTS OF INTEREST

The author has no competing interest to disclose

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