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Engineered Virus to Treat Lipoprotein Lipase Deficiency

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Abbreviations: ADA: adenosine deaminase ; EU: European Union

Gene therapy, through positive results and setbacks, has reached one of its peaks when the European Commission granted its approval for Glybera to be marketed in European Union in November 2012 as the first commercially-approved gene therapy product in the West. Since the first clinical trial with a gene therapy intervention was carried on in 1990 (Table 1), this is a remarkable achievement. It was not a simple result, given the lengthy and tortuous way through which it was obtained [1]. The various steps, including the pre-clinical and clinical studies that have brought to this decision, have been recently critically reviewed by Bryant and colleagues [2] and the identification of the viral vector as well as the first steps in animal models has been narrated by principal investigators [3].

Two decades of 'try and error' efforts have been now crowned with success by the Glybera marketing. Actually, the concept of gene therapy was advanced by the Nobel laureate in Physiology or Medicine David Baltimore in 1978 concerning the insertion of a normal gene into precursors cells from bone marrow to cure blood diseases [4]. It took twelve years to see the first clinical trial in human beings, and after that one other 1700 clinical trials have been carried on worldwide [5]. The 1990 trial was conducted on two children with a severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID) by the infusion of their own T cells engineered *ex-vivo* by a retrovirus expressing ADA [6]. Although the results were not astonishing (one child responded temporarily, and the other presented a fair less response), clinicians and researchers were confident that a revolution in medicine was approaching. This boom was arrested with the death of 18-year old Jesse Gelsinger in 1999, who was taking part of a gene therapy clinical trial aimed at treating deficiency of ornithine transcarbamylase. Unfortunately, his immune system reacted badly to the attenuated recombinant adenovirus used for liver transduction determining a multi-organ failure [7]. However, despite this ignominious result, gene therapy interventions have gained increased attention, so that to date cancer composes over 60% of all ongoing clinical gene therapy trials worldwide, followed by monogenetic and cardiovascular diseases [5]. Among the monogenic diseases, positive results have been obtained for Leber's congenital amaurosis,β-thalassemia, X-linked severe combined immunodeficiency (SCID-X1), ADA-SCID, haemophilia B, and Wiskott-Aldrich syndrome. The most used vectors for vehicling the therapeutic genes and engineering of cells *ex-vivo* or tissues *in vivo* are plasmid DNA, adenovirus, and retrovirus.

Glybera (alipogene tiparvovec) is an adeno-associated viral (AAV) vector engineered to express a variant of lipoprotein lipase (LPL) endowed with hyperactivity (LPL^{S447X}). AAV is a non-pathogenic, single stranded DNA virus, whose genome is comprised of two genes, *rep* and *cap*, flanked by two inverted terminal repeats (ITRs). The vector used in the treatment of LPL deficiency is an hydrid one, bearing the Cap protein from AAV serotype 1 and ITRs from AAV2 [8]. The AAV1 was chosen for the Cap function because of low seroprevalence in normal human beings and because AAV1 transduced skeletal muscle with higher efficiency than AAV2 [9]. Importantly, while wild-type AAV eventually integrates into chromosome 19 [10], the recombinant AAV vector is non-integrating, persisting as episomal concatamers in the transduced cells [11], so avoiding in principle the risk of insertional oncogenesis, although also in the case of AAV vectors a low rate of random integration has also been found [12].

Year	Milestone
1978	The idea of gene therapy is launched by David Baltimore
1990	First clinical trial of gene therapy in ADA patients
1999	Death of Jesse Gelsinger for a gene therapy intervention
2012	Approval of Glybera for marketing in the EU

Table 1: Main positive and negative milestones in gene therapy.

This AAV vector was proved to be efficacious in pre-clinical LPL deficient animal models (mice and cats) and finally in patients with LPL deficiency. This autosomal recessive disorder is considered an ultra-orphan disease affecting just 1 person per million (ultra-orphan diseases are defined as having a prevalence of equal or less than 0.1 per 10,000 persons in the European Union [13]). In these patients, chylomicrons cannot be metabolized correctly by the skeletal muscle and adipose tissue in free fatty acids, ensuing in hyper triglyceridemia and hyper chylomicronemia which, in turn, is associated with severe pancreatitis. The currently accepted treatment, i.e. fat dietary restriction, does not allow to substantially decrease serum tryglicerides, making gene therapy interventions ethically acceptable in these very rare patients. The clinical trials, however, did demonstrate a partial clinical effectiveness, also for the lack of standardised surrogate end-points to which benchmark the outcome. Other flaws that will constrain the evaluation of Glybera are the limited number of patients to be included in the clinical evaluation for long times (in the last study published, 14 patients were studied for 2 years [14]), so to evaluate the efficacy and, importantly, the safety of this treatment. Nevertheless, Glybera approval for marketing in the EU represents a milestone in gene therapy and propulsion for scientists and biotech companies working in this field, and will prompt further studies in gene and cell therapy for monogenic diseases.

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