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The Firsts in the Chronicle of Gene Therapy: Triumphs and Tragedies in Treating Inherited Disorders

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This review chronicles the pivotal "firsts" in gene therapy, from early successes like the 1990 *ex vivo* trial for adenosine deaminase-deficient severe combined immunodeficiency (ADA-SCID) to the profound setbacks that shaped its trajectory. Tragic events, including leukemia from insertional mutagenesis in SCID-X1 trials and the death of Jesse Gelsinger from a catastrophic immune response, forced a critical re-evaluation of vector safety and regulatory oversight.
This introspection led to the development of safer adeno-associated virus (AAV) vectors and the landmark success of *in vivo* therapy with Luxturna for Leber's congenital amaurosis. The path to commercial viability saw the failure of Glybera contrasted with the blockbuster success of Zolgensma for spinal muscular atrophy, paving the way for the current era of CRISPR-based gene editing with the approval of Casgevy. This history reveals a field matured through adversity, now delivering transformative therapies while still facing critical challenges in cost, immunogenicity, and long-term durability.

Key words: Gene therapy, Adverse events, Genetic disorders

REVIEW ARTICLE

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INTRODUCTION: FROM CONCEPT TO CLINIC

The idea of correcting defective genes has long been the ultimate ambition of genetic medicine. Ever since the discovery that genetic information resides in the threads of nucleic acid—and that minute errors within it can profoundly impact human health—the great minds of science have been irresistibly drawn to finding a way to patch these flaws.

However, the "find-and-fix" concept proved far more complex than early optimism suggested. The field lacked efficient vectors to deliver genes to target tissues and a deep understanding of the immune system, which is inherently resistant to any foreign genetic material. As technology advanced to overcome these biological hurdles, the regulatory paradigm also had to evolve to oversee unprecedented studies on human subjects.

EARLY DAYS OF GENETIC ENGINEERING

In the 1950s, the DNA double helix was first identified as the core genetic material. It was found to replicate itself, with its information transcribed into RNA and then translated into protein by elaborate cellular machinery. The following decades brought foundational discoveries in molecular biology, enabling scientists to isolate, multiply, analyze, and recombine DNA sequences. A landmark achievement occurred in 1978 when recombinant human insulin was produced using *E. coli* bacteria expressing the human insulin gene [1].

By the 1980s, genes responsible for Mendelian diseases began to be cloned,

starting with X-linked chronic granulomatous disease and Duchenne muscular dystrophy, followed by cystic fibrosis and Huntington's disease. Since many of these conditions were caused by a loss of gene function, delivering a functional copy of the missing gene seemed a straightforward and irresistible challenge for enthusiastic researchers.

FIRST SUCCESSFUL GENE THERAPY: SEVERE COMBINED IMMUNODEFICIENCY (ADA-SCID)

Adenosine deaminase (ADA) deficiency is a rare genetic disorder that devastates the immune system, falling under the umbrella of severe combined immunodeficiency (SCID). The ADA enzyme is responsible for breaking down deoxyadenosine, a substance toxic to lymphocytes. Patients with ADA-SCID are susceptible to recurrent, life-threatening infections, with treatment options limited to bone marrow transplantation and enzyme replacement therapy.

Ashanthi DeSilva, diagnosed with ADA-SCID at age two after recurrent infections. Enzyme replacement therapy with pegylated ADA incompletely recovered her immune system. A matching bone marrow donor could not be found. In 1990, at four years old, she was enrolled in a landmark gene therapy trial, which was meticulously prepared for several years [2]. The treatment was an *ex vivo* gene therapy: her T lymphocytes were obtained via apheresis, expanded in culture, and transduced with a retroviral vector carrying a functional *ADA* gene. These corrected cells were then reinfused into her bloodstream [3].

The therapy was a remarkable success. The engineered T-cells began producing the ADA enzyme, significantly improving Ashanthi's immune function. The T-cells outlived much longer than expected. Although she continued to receive supplemental enzyme replacement therapy, the gene therapy allowed her to lead a normal life, becoming a genetic counselor.

Despite this initial triumph, subsequent trials using similar or more advanced technologies failed to replicate the same degree of success. However, the pioneering work led to the 2016 EMA approval of Strimvelis, an autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with the retroviral vector that encodes for the human ADA cDNA sequence. It is the first *ex vivo* gene therapy approved for clinical use.

FIRST CANCER CAUSED BY GENE THERAPY: SCID-X1

Another type of SCID, popularized by the "bubble boy" of the 1970s, is caused by defects in the *IL2RG* gene on the X chromosome and is known as SCID-X1. Researchers in Paris (1999) and London (2001) devised similar *ex vivo* gene therapy trials, but with a key difference: they transduced hematopoietic stem cells from bone marrow with a retrovirus carrying the *IL2RG* gene.

The immunologic outcomes were initially successful, with treated infants recovering functional immune systems [4] that lasted for over a decade [5]. Tragically, this success was overshadowed when six of the 19 subjects developed T-cell acute lymphoblastic leukemia 2-14 years after treatment, which was fatal in one case. The cause was insertional mutagenesis: the retroviral vector integrated into the host genome near a proto-oncogene, *LMO2* for example, activating it and leading to the uncontrolled growth of T-cells. This devastating adverse event halted many gene therapy trials and spurred the development of safer vectors, such as self-inactivating retroviruses and lentiviruses [6].

FIRST DEATH CAUSED BY GENE THERAPY: THE CASE OF JESSE GELSINGER

Ornithine transcarbamylase (OTC) deficiency is an X-linked disorder of the urea cycle, which metabolizes toxic ammonia into urea for excretion. The resulting hyperammonemia is devastating to the brain, and neonatal-onset cases have a grim prognosis.

Jesse Gelsinger was an 18-year-old with a milder, late-onset form of OTC deficiency. He lived a relatively normal life managed with a low-protein diet and numerous medications, though he had experienced several metabolic crises that required interventions. In 1999, he enrolled in a Phase 1 clinical trial at the University of Pennsylvania, which used an adenovirus vector to deliver the *OTC* gene. Seventeen other subjects had been treated before him.

The day before his injection, Jesse's ammonia levels were elevated, but this was overlooked as it was not an explicit exclusion criterion. The day after the infusion, he developed jaundice and rapidly deteriorated into a coma, to expire in four days.

It was only after his death that his family learned of critical undisclosed information: monkeys had developed severe liver

damage in preclinical studies, other human subjects had experienced serious adverse events, and the principal investigator had a significant financial stake in the company developing the therapy [7]. Jesse's tragic death became a watershed moment, forcing a field-wide reckoning that led to intense scientific introspection and the implementation of much stricter regulatory oversight [8].

FIRST SUCCESSFUL *IN VIVO* GENE THERAPY: LEBER'S CONGENITAL AMAUROSIS

A major breakthrough occurred in 2008 with the success of an *in vivo* gene therapy for Leber's congenital amaurosis (LCA), a rare form of inherited blindness [9,10]. The treatment involved a subretinal injection of a recombinant adeno-associated virus (AAV) carrying a functional *RPE65* gene. The therapy was highly effective, and because the subretinal space is immunologically privileged, patients did not suffer from significant immune reactions.

The AAV vector proved to be an ideal delivery vehicle. It is less immunogenic than adenovirus, and its linear genome can be almost entirely replaced with a transgene. Its integration into the host genome is minimal compared to retroviral vectoral vectors, remaining predominantly episomal, though integration at DNA break sites has been documented. The therapy, later named voretigene neparvovec (Luxturna), was highly effective, providing life-changing benefits by restoring functional vision to patients with near-total blindness. It was approved by the FDA in 2017 and the EMA in 2018.

FIRST *IN VIVO* GENE THERAPY APPROVAL AND FIRST COMMERCIAL WITHDRAWAL: GLYBERA

Alipogene tiparvovec (Glybera) was a gene therapy for lipoprotein lipase (LPL) deficiency, a rare disorder caused by biallelic mutations in the *LPL* gene. It used an AAV vector to deliver a hyperfunctional variant of the *LPL* gene via multiple intramuscular injections [11,12]. The therapy reduced the frequency of pancreatitis without major adverse events and received clinical approval from the EMA in 2012, making it the first *in vivo* gene therapy approved in the Western world.

Despite its clinical promise, Glybera was a commercial failure. Its million-dollar price tag for a one-time treatment proved prohibitive. Only one person received the drug commercially before the company abandoned its marketing authorization in 2017. The remaining three doses were given to patients with a nominal price of one euro.

FIRST COMMERCIALLY SUCCESSFUL GENE THERAPY: ZOLGENSMA

Onasemnogene abeparvovec (Zolgensma) is an AAV-mediated gene therapy for spinal muscular atrophy (SMA), a devastating neuromuscular disorder caused by the absence of the *SMN1* gene [13]. First approved by the FDA in 2019, it has since become a global blockbuster.

Delivered as a single intravenous infusion, Zolgensma is a systemic *in vivo* gene therapy that provides a functional copy of the *SMN1* gene to motor neurons. To enhance its efficacy, the transgene was packaged in a self-complementary form, enabling more efficient expression. Despite its multi-million-dollar price, more than 3,700 babies with SMA have been treated. Its use, however, remains restricted to children under two years of age, as its safety and efficacy have not been formally established in older patients.

FIRST SERIOUS IMMUNE REACTION TO A TRANSGENE: DUCHENNE MUSCULAR DYSTROPHY

Duchenne muscular dystrophy (DMD) has long been a target for gene therapy. The *dystrophin* gene, which is defective in DMD, is too large to fit into an AAV vector. Researchers cleverly engineered a miniaturized version, microdystrophin, that could be packaged for delivery.

Several companies advanced clinical trials using AAV-mediated systemic delivery of microdystrophin. They were delivered intravenously as the primary target is skeletal muscles of the whole body and cardiac muscle. However, the high vector doses in older children led to numerous serious adverse events, including atypical hemolytic uremic syndrome, thrombotic microangiopathy, and, most recently, fatal liver failure. A particularly concerning side effect was transgene-induced myositis [14].

In a remarkable act of collaboration, competing companies shared their data to investigate the cause of myositis. They discovered that specific regions of the microdystrophin transgene were highly immunogenic, triggering a T-cell response in boys whose own mutations resulted in the complete absence of those corresponding regions in their native dystrophin protein [15].

FIRST GENE-EDITING THERAPY: CASGEVY

Exagamglogene autotemcel (Casgevy) is the first approved therapy based on CRISPR gene editing. It is an *ex vivo* treatment for beta-thalassemia and sickle cell disease. The process involves collecting a patient's hematopoietic stem cells, using electroporation to deliver the CRISPR-Cas9 system that disables the *BCL11A* gene. This gene acts as a switch that turns off fetal hemoglobin production after birth. By disabling it, the edited cells are induced to reactivate the production of functional fetal hemoglobin. After the patient undergoes myeloablative chemotherapy to clear their bone marrow, the edited cells are reinfused [16].

While often hailed as a personalized treatment, the gene-editing strategy itself is uniform, targeting the same *BCL11A* gene in all patients to achieve a common therapeutic outcome.

CONCLUSION: HURDLES AND HOPES

The landmarks detailed above represent a fraction of the events that have shaped the field of gene therapy. Significant hurdles remain, including the prohibitive cost of treatments, the challenge of conducting trials for ultra-rare disorders, and the need to tame the immune response to vectors and transgenes. Neutralizing antibodies can prevent initial treatment or re-dosing, and the long-term durability of these therapies remains unknown.

More challenges will undoubtedly emerge. Nevertheless, the relentless progress in this field signals an unwavering commitment to fighting against genetic determinism and offering hope where there was none.

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