CHAPTER 11

Gene Therapy Clinical Trials: Past, Present and Future

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INTRODUCTION

Gene therapy is a medical technique that involves inserting one or more corrective genes that have been designed in the laboratory into patient cells to treat a disease. To do this, medicinal products are used that are defined as gene therapy medicinal products.

On the wave of recombinant DNA pioneering studies and related ethical discussions of early 1970s, in 1972, Friedmann and Roblin (1972) published a paper in Science which cited Stanfield Roger's proposal in 1970 that 'good DNA' could be used to replace defective DNA in people with genetic disorders. They also proposed that development and clinical application of gene therapy techniques should be guided by ethical and scientific criteria so as to ensure that gene therapy is used without prejudice to patient's safety and to progress of science.

Those pioneering thoughts have evolved through the decades into regulatory science applied to clinical development of advanced therapies. Regulatory authorities all around the world have issued requirements and guidance to control the development and use of medicinal products for gene therapy approaches. An overview of the regulations that have so far been applied to clinical development and market approval of gene therapy is out the scope of this chapter; a comprehensive discussion can be found in 'Regulatory Aspects Of Gene Therapy And Cell Therapy Products: A Global Perspective' (Galli, 2015).

It took several years to move from those initial thoughts to a practical application. The advent of improved gamma-retroviral vectors (RVs) with enhanced gene transfer efficiency and stable integration into the chromosome (Armentano et al., 1990; Gilboa, 1986; Miller and Buttimore, 1986; Miller and Rosman, 1989) and the demonstration that this procedure of gene transfer could be effectively and safely used in humans (Kasid et al., 1990; Rosenberg et al., 1990; Anderson, 1992) allowed the development of gene therapy clinical trials in the United States and Europe (Wolff and Lederberg, 1994).

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THE MAIN TYPES OF GENE THERAPY VECTORS AND THEIR MODES OF DELIVERY

A variety of different vectors have been applied in gene therapy trials, among which two main categories can be identified: viral and nonviral vectors. Treatment strategies are based on in vivo administration (i.e., injecting the vector directly into a patient's body) or on ex vivo manipulation of human cells that are firstly genetically modified in vitro with the vector and then administered to the patient.

All vectors, independently from their origins or from the in vivo or ex vivo use, are constructed to contain a backbone with the function of delivering to target cells and an expression cassette with the function of coding for the transgene with the desired clinical efficacy.

Nonviral approaches include modified or naked DNA, or mRNA which can be delivered to the target cell by physical or chemical methods. Physical gene delivery strategies include microinjection, needle injection, jet injection, gene gun/DNA injection/DNA-coated particle bombardment, electroporation, sonoporation, magnetofection (Jin et al., 2014; Wang et al., 2013; Manjila et al., 2013; Nayerossadat et al., 2012).

Chemical gene delivery methods are based on calcium phosphate precipitation or on the ability of polycations, cationic lipids or lipopolyplexes to complex nucleic acids via charge interaction, leading to the formation of particles comprising the DNA/RNA (Jin et al., 2014; Wang et al., 2013; Medina-Kauwe et al., 2005).

A number of advantages can be considered by using nonviral vectors such as low immunogenicity, easy scale-up production and the ability to deliver large molecular size genes. However, delivery efficiency can be affected by an inefficient uptake as nonviral vectors can be easily degraded intracellularly or extracellularly. Other disadvantages are represented by low gene expression and low efficacy, due to gradual dilution of episomal DNA in dividing target cells (Wang et al., 2013). This approach has been used for gene therapy of cardiovascular diseases (Taniyama et al., 2012) or in solid tumours (Thaker et al., 2017; Spanggaard et al., 2017); however, results attained there have not been encouraging. Generally, nonviral vectors are not able to integrate into the cellular genome, thus persisting into the cells as episomal entities (Hitt et al., 1995). However, they can be engineered as to contain transposons or other mobile DNA elements that stably integrate the therapeutic gene into the target cell chromosomes (VandenDriessche et al., 2009; Tipanee et al., 2017). The use of nonviral vectors containing the latest generation of transposons has been proposed for clinical application mainly in cancer immunotherapy (Hudecek et al., 2017).

Viral vector delivery technologies use a modified virus as a carrier to deliver the target gene. Different viral vector families have been investigated such as Adenovirus (AdV), Adeno-Associated Virus (AAV), Herpes Simplex Virus (HSV), Retrovirus (RV) (Gammavirus and Lentivirus (LV)), Vaccinia and Baculovirus (Bessis et al., 2004; Choudhury et al., 2017; Verlengia et al., 2017).

High cellular uptake and transduction efficiency are the main advantages of this type of vectors, but there are safety concerns associated with their use. Due to their biological characteristics, viral vectors can elicit inflammatory or immune responses that may impair long-term gene expression and raise safety concerns (Manno et al., 2006) or when integrating into cell genome can result into insertional oncogenesis (Hacein-Bey-Abina et al., 2008, 2003a).

To overcome those inherent defects, viral vector design has been progressively improved so that most of the viral vectors currently in clinical use are chimeras that share very few sequences with the parental viruses. For instance, delivery efficiency or selectivity can be improved by pseudotyping viral capsids as for AAV (Hastie and Samulski, 2015), or vector-related risks can be mitigated by deleting most of unnecessary sequences as for Lentiviral Vector (LVV) (Naldini, 2011). Those vector-engineering methods aim at enhancing vector safety while retaining the desired biological characteristics for clinical efficacy.

The vast majority (81.5%) of gene therapy clinical trials to date have addressed cancer, cardiovascular disease and inherited monogenic diseases (Ginn et al., 2013): the first two because of their prevalence, impact and potentially fatal outcomes, the latter because the concept of replacing a well-defined defective gene with its correctly functioning counterpart with the aim to ensure permanent correction has an enormous appeal.

THE EARLY DAYS

The gene therapy trial history starts with two unapproved trials in the early 70s and 80s (Wolff and Lederberg, 1994). In the first trial, two young girls with arginase deficiency syndrome were treated in vivo with a wild-type Shope papilloma virus to replace the missing viral arginase enzyme. In the second trial, marrow cells from two patients with β-thalassaemia were treated ex vivo with a β-globin-containing plasmid before being transplanted again into the patients by a bone marrow (BM) transplant. Both trials were stopped. In neither case was there any real follow-up reported.

The first human gene therapy protocol for treating severe combined immunodeficiency disease (SCID) due to adenosine deaminase (ADA) deficiency with autologous lymphocytes transduced with a human ADA gene was submitted for approval in 1990 (Blaese and Anderson, 1990) and published in 1995 (Blaese et al., 1995). The trial involved ex vivo gene transfer to umbilical cord blood cells or autologous T lymphocytes of children with SCID due to mutations in the ADA-coding gene (Blaese et al., 1995; Bordignon et al., 1995; Kohn et al., 1995). In those early studies, gene transfer protocols based on a murine RV were inefficient to transduce haematopoietic stem cells (HSCs), thereby limiting extent and duration of gene transfer.

However, those ex vivo studies demonstrated for the first time the feasibility of using RV vectors for the transduction of human lymphocytes.

In the following years, clinical gene therapy approaches tried to establish what were the best vectors to use and to explore their safety, while looking for clinical experience in genetic diseases, such as cystic fibrosis, or in cancers where an effective therapy is still missing, such as glioblastoma. The most used vectors were RVs and AdVs, and most applications were in oncological patients or genetic diseases (DeWeese et al., 2001; Kirn, 2001; Thomas et al., 2003; Greco and Dachs, 2001; Kochanek, 1999; Maatta et al., 2009), but plasmids (so called DNA vaccines) were also used (Alton et al., 1999; Mor et al., 1997; Tighe et al., 1998). As stated above, viral and nonviral vectors used were only able to add a genetic sequence into target cells that bear the defective gene. Apart from genetic diseases where the gene to be targeted is well known, approaches for gene therapy of cancer mostly targeted mutated proteins that were very popular at that time, such as p53, or used a suicide strategy aiming at selectively killing cancer cells. None of those approaches proved to be effective at the clinical level, and none of the investigational medicines involved in those trials were further developed and later approved by Food and Drug Administration (FDA) or European Medicines Agency (EMA) (News, 2010). A remarkable exception is Gendicine (Editorial, 2005; Peng, 2005), an AdV vector derived from Adenovirus type 5 (AdV5) and engineered to express p53, that was market approved by China FDA for the treatment of head and neck squamous cell carcinoma. This product was totally unknown in the western world as the data were all published in Chinese journals. Recently, an update on the clinical experience of Gendicine used in association with oncological standard therapy has been published (Zhang et al., 2018).

While clinical experience with gene therapy progressed, immune responses and insertional mutagenesis emerged as main concerns, particularly in light of the poor clinical efficacy found.

In 1999, a fatal event occurred when an 18-year-old boy suffering from ornithine transcarbamylase (OTC) deficiency, an X-linked genetic disease of the liver, died when treated with gene therapy (Somia and Verma, 2000; Raper et al., 2003). The investigational medicine was a replication defective AdV vector based on AdV5 expressing human OTC. The patient was included in the very high-dose treatment group via hepatic artery. The death was attributed to unexpected and devastating inflammatory reactions to the AdV vector. In January 2000, the US FDA put that trial on hold and several other trials were also halted (Sibbald, 2001).

Meanwhile, a very promising approach to gene therapy was coming from the clinical experience with BM transplantation: ex vivo transduction of BM cells.

A clinical trial started in France, where children suffering from a rare form of X-linked severe combined immunodeficiency (SCID-X1) were successfully treated with autologous BM cells transduced with an RV vector carrying the correct gene (Cavazzana-Calvo et al., 2000).

However, in 2002, a series of severe adverse events occurred as leukaemia developed late after gene therapy (at 23–68 months posttreatment; (Cavazzana, 2014)) in 4 out of

10 children in the French trial and 1 out of 10 children in a similar UK trial. The leukaemia was fatal in one patient but was cured in others. It was later found out to be caused by RV insertional oncogenesis (Hacein-Bey-Abina et al., 2008, 2003b; Howe et al., 2008). Nevertheless, efficacy of the gene therapy treatment in those SCID-X1 children was evident, as they achieved a stable immunological T cell compartment (Cavazzana, 2014).

Thus, the first SCID-X1 gene therapy trial not only provided proof of principle on the clinical feasibility of gene therapy but also highlighted the significant toxicity associated with the Long Terminal Repeat (LTR) strong enhancer effect on the RV vector used to transduce BM cells. Leukaemic T cell clones showed vector integration near the LMO2 proto-oncogene promoter leading to its aberrant transcription and expression (Hacein-Bey-Abina et al., 2008, 2003b). A similar proto-oncogenes activation caused by Murine Leukemia Virus (MLV)-derived RV integration was also later reported for Wiskott–Aldrich and chronic granulomatous disease patients treated with a similar gene therapy approach (Stein et al., 2010; Avedillo Díez et al., 2011).

It should be noted that integration-related toxicity is also linked to other characteristics of the gene therapy medicinal product (such as target cell nature and patient genetic background), as it was shown in different Italian clinical trials: in ADA-SCID patients treated with a similar gene therapy approach (but a different transgene) (Aiuti et al., 2007, 2009; Cicalese and Aiuti, 2015; Ferrua and Aiuti, 2017), in patients with high-risk haematological diseases treated with transduced T lymphocytes (Lupo-Stanghellini et al., 2010; Cieri et al., 2014) and in autologous genetically modified cultured epidermal stem cells for gene therapy of junctional epidermolysis bullosa (De Rosa et al., 2014). Those clinical trials were carried out in the same years as the French trial; none of those patients have experienced vector-related genotoxicity.

Due to the leukaemia events, the French SCID-X1 clinical trial was halted like many others in the European Union and in the United States in early 2000s, while the cause was investigated. An in-depth analysis of RV insertion sites was initiated, resulting into a wealth of research on molecular methods to track integration and study its effects (Schmidt et al., 2001; Schröder et al., 2002; Montini et al., 2009; Biasco et al., 2011; von Kalle et al., 2014). It was shown that the RV insertion pattern is not random, and MLV-derived vectors integrate preferentially in transcriptionally active promoters and regulatory regions (Laufs et al., 2004).

Those serious adverse events had the effect to slow down gene therapy clinical development, but being the proof of principle established, they also led to a worldwide effort to improve integrating vector safety. Regulatory authorities too reacted to those events, issuing guidance documents such as the EMA

Reflection paper on management of clinical risks deriving from insertional mutagenesis (EMA, 2012; Aiuti et al., 2013).

TIME FOR SUCCESS

While the experience with SCID-X1 was also showing limited clinical efficacy because of the small proportion of engrafted genetically corrected HSCs, indeed a breakthrough was achieved when successful gene therapy pilot studies conducted in Italy at San Raffaele Telethon Institute for Gene Therapy (SR-Tiget) introduced an improved gene transfer protocol for BM haematopoietic stem and progenitor cells and the use of non-myeloablative chemotherapy regimen prior to gene therapy to prepare space for the transduced progenitors in the BM (Aiuti et al., 2002). As none of the patients received concurrent enzyme replacement therapy (ERT), the efficacy of gene therapy as single treatment could be fully assessed, exploiting at the same time the growth advantage for ADA-transduced cells. Following those initial studies, results were confirmed and extended in another clinical trial conducted at SR-Tiget. Gene therapy resulted in sustained lymphoid reconstitution with gene-corrected T cells, improvement of immune functions and effective metabolic detoxification in the absence of adverse events related to gene therapy (Aiuti et al., 2009; Cicalese et al., 2016), and most importantly, as described above, there were no severe adverse events linked to target cell transduction. Similar results were obtained in another set of patients (Gaspar et al., 2011).

The same success was met by the Italian clinical trials with the suicide gene therapy in allogeneic haematopoietic stem cell transplantation (HSCT) (Lupo-Stanghellini et al., 2010; Cieri et al., 2014).

In 2016, the EMA granted marketing approval to the medicinal products used in those pioneering clinical trials, thus recognising their efficacy and safety: Strimvelis received EU market approval for patients affected by ADA-SCID without a suitable human donor, and Zalmoxis received EU market approval for patients affected by leukaemia or lymphoma who have received a haploidentical HSCT (EMA, 2012; Aiuti et al., 2017). Up to 2013, RV and AdV vectors were the most popular gene therapy approaches, having been used in approximately two-thirds of trials performed (Ginn et al., 2013).

After the serious adverse events in the French SCID trial, there was a decrease in the proportion of trials using RV: in 2012, only 19.7% of trials compared with 22.8% in 2007 and 28% in 2004 (Ginn et al., 2013).

RV preference for integration into the first introns of genes and transcriptional start sites still is a cause of concern, if used for transducing cells with proliferation potential.

Therefore, efforts have been shifted towards the development of new vectors where safety, in terms of low genotoxicity and immunogenicity, would combine with a high efficiency of delivery. Although AdV vectors continued to be developed for anticancer treatments, LV and AAV soon emerged as promising technological tools.

LV vectors were developed to overcome the inability of RV vectors to infect nondividing cells (Naldini et al., 1996a). LV such as Human Immunodeficiency Virus (HIV) do not require cell division for gene transfer and are capable of integrative transfection of several quiescent and postmitotic cell types as well as proliferating cells (Naldini et al.,

1996a,b). Nevertheless, due to the genotoxicity risk posed by their integration ability, the use of LV vectors for gene therapy has been so far mainly limited to ex vivo transduction of haematopoietic cells, where they have shown high levels of gene transfer and transgene expression in haematopoietic progenitors (Naldini, 2009; Sessa et al., 2016; Biffi, 2017; Piguet et al., 2017). With this approach, several trials have been initiated in X-linked adrenoleukodystrophy (Cartier et al., 2009), in beta thalassaemia (Cavazzana-Calvo et al., 2010; Ferrari et al., 2017; Lidonnici and Ferrari, 2018), in Wiskott–Aldrich syndrome (Morris et al., 2017), in lysosomal storage diseases (Penati et al., 2017) showing significant clinical benefits without so far any major adverse event, although a case of major clonal expansion has been reported (Cavazzana-Calvo et al., 2010).

A very important application of gene vector technologies to ex vivo cell transduction is the development of Chimeric Antigen Receptor (CAR) T cells for cancer therapy (Hartmann et al., 2017). A comprehensive discussion of the clinical trials with CAR-T cells can be found elsewhere in this book.

Up to 2012, AdVs were the most commonly used vectors (23.3%) (Ginn et al., 2013). AdVs can carry a larger DNA load than RV, but their capacity is still too small to accommodate the genes required for certain clinical applications. The main advantages of AdV vectors are their high transduction efficiency, high gene expression level and ability to infect nondividing cells. As they remain episomal (i.e., they do not integrate into the cell genome, therefore are devoid of the genotoxicity risk), the transgene expression declines fairly rapidly in dividing cells, so that successive doses are needed to obtain a clinical effect. However, as most people are seropositive to the most common AdVs, preexisting immunity may impair clinical efficacy (Verma and Somia, 1997). Another important safety issue is the possibility of provoking severe immune and inflammatory responses as it was tragically exemplified in the case described above (Jonsson and Kreppel, 2017).

The risk of unwanted immunological responses can be reduced by choosing viruses with low immunogenicity such as AAV. In addition, nonintegrating AAV can reduce the risk of insertional oncogenicity associated with integrating viruses. Target specificity can be increased by engineering the viral capsids with different peptides to select the target cell receptor. High efficiency of in vivo gene transfers to numerous cell types, and the development of a large arsenal of viral capsids with different tropism and low innate/inflammatory responses to viral particles have made these vectors very attractive (Hastie and Samulski, 2015).

AAV offers significant advantages over AdV and RV as a platform for therapeutic gene transfer, particularly with regard to safety considerations (Dismuke et al., 2013). Within the past several years, evidence of clinical efficacy for AAV vectors in the treatment of monogenic disorders has emerged (Hastie and Samulski, 2015). Notable examples include the use of AAV for the treatment of factor IX hemophilia (Nathwani et al., 2011; Nathwani et al., 2017; George et al., 2017), cystic fibrosis (Griesenbach et al., 2015), inherited diseases of liver metabolism (Castello et al., 2016) and retinal disorders (Maguire et al., 2008; Le Meur et al., 2018; Russell et al., 2017; Trapani et al., 2015; Kumaran et al., 2018). AAV have been also used in gene therapy approaches to heart disease (Penny and Hammond, 2017).

AAV-based gene therapy medicinal products have proven so far the most successful among vectors for in vivo use, as there are two market-approved medicines in EU and in United States based on AAV.

Glybera (alipogene tiparvovec, an AAV vector expressing lipoprotein lipase) was the first gene therapy product approved by EMA in 2012 for the treatment of a very rare monogenic disease (lipoprotein lipase deficiency) (Bryant et al., 2013).

Very recently, FDA has approved LUXTURNA (voretigene neparvovec-rzyl), an AAV vector indicated for the treatment of patients with confirmed biallelic *RPE65* mutation–associated retinal dystrophy (Maguire et al., 2008; FDA).

In the vast majority of clinical trials described so far, replication defective vectors have been used to mitigate the risk of dissemination to nontarget tissues (including the germ line) or horizontal transmission. However, replication competent vectors have been used in clinical trials exploiting their oncolytic effect (Duffy et al., 2017; Hamid et al., 2017; de Graaf et al., 2018). One of them has successfully obtained a market authorisation: Imlygic (talimogene laherparepvec) was approved in the EU and United States for the treatment of unresectable melanoma. It is a HSV type 1–derived oncolytic immunotherapy designed to selectively replicate within tumours and produce granulocyte macrophage colony–stimulating factor to enhance systemic antitumour immune responses (Andtbacka et al., 2015).

The milestones in gene therapy development are summarised in Fig. 11.1.

THE SECOND INNOVATION WAVE

All vectors (viral and nonviral) used so far for gene therapy clinical approaches are only able to add a genetic sequence into target cells that bear the defective gene.

A recent significant advance is targeted genome editing (Mussolino et al., 2017). This technology allows to correct a specific sequence within a genomic DNA region. Gene editing has a great potential for gene therapy, although evidence is still accumulating on its precision (i.e., off-target mutations) and ethical concerns exists due to potential genetic changes in germline cells.

Three important strategies have been developed based on zinc-finger nuclease (ZFN), transcription activator-like effector nucleases (TALENs) and clustered regularly interspaced short palindromic repeat (CRISPR)/CRISPR-associated protein 9 (CRISPR/Cas9) (Sander and Joung, 2014). A more detailed discussion on those technologies can be found elsewhere in this book.

The first clinical trial using a nuclease for targeted gene editing was conducted in HIV patients with autologous CD4-enriched T cells modified at the CCR5 gene locus by ZFN (Tebas et al., 2014). This strategy was also used for the treatment of cervical cancer, hemophilia B and mucopolysaccharidoses (Cornu et al., 2017).

The TALEN technology was used for the treatment of an 11-month-old baby with B acute lymphoblastic leukaemia. This was the first patient treated with TALEN engineered

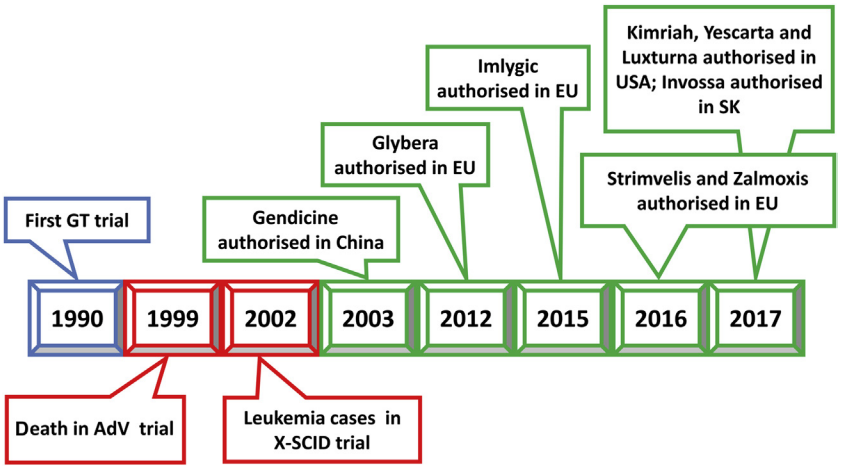

Figure 11.1 Overview of the gene therapy medicinal products that have been granted market authorisation.

CAR19 T Cells (Qasim et al., 2015). TALENs technology has also been used for the correction of COL7A1 gene involved in epidermolysis bullosa (Osborn et al., 2013).

Many potential applications of gene editing with CRISPR/Cas9 are currently under development. A first clinical trial using CRISP/Cas9 technology was authorised in China in lung cancer patients and others similar in prostate, bladder and kidney cancer were announced (Cyranoski, 2016). Other clinical trials have been started in other regions of the world (Ginn et al., 2018).

PERSPECTIVES

Gene therapy for ADA-SCID, AAV gene therapy for eye disease and LV vector platform is the most significant success stories to date, but progress in many other areas has been significant and will hopefully result in additional approvals in the near future.

After decades of clinical trials, after the first frustrating unsuccessful trials and after many clinical successes over the past recent years, gene therapy has been proven to provide long-lasting benefits to patients, thus resulting into an important tool for patient treatment.

Due to the novelty of development approach as compared with traditional pharmaceuticals and the challenges thus posed to all actors in the field (scientists, industry, regulators) (CAT, 2010), gene therapy has also been pivotal in establishing a new paradigm for collaboration between academia, industry and regulators that has been instrumental in driving the field ahead (Maciulaitis et al., 2012).

Nowadays some gene therapy medicinal products are approved for the market (Table 11.1): Glybera, Strimvelis, Imlygic, Zalmoxis, YESCARTA, Kymriah, LUXTURNA,

Table 11.1 Approved Gene Therapy Medicinal Products.

GTMP Commercial Name (INN)	Type of GTMP	MA Holder	Clinical Indication	MA Date	MA Authority	Note
Gendicine	Ad-p53	Shenzhen Sibiono GeneTech	Head and neck squamous cell carcinoma	2003	China FDA	
Glybera (alipogene tiparvovec)	AAV LPLS447X	UniQure	Lipoprotein lipase deficiency	2012	EMA	Withdrawn from EU market
Imlygic (talimogene laherparepvec)	OncolyticGM–CSF–HSV-1	Amgen	Metastatic melanoma	2015 2015	EMA US FDA	
Strimvelis	Autologous CD34+ cells genetically modified with RV-ADA	GSK	ADA-SCID	2016	EMA	
Zalmoxis	Allogeneic T cells genetically modified with RV-ΔLNGFR+ HSV-TK Mut2	MolMed		2016	EMA	
KYMRIAH (tisagenlecleucel)	Autologous CD19-CAR-T cells	Novartis	Relapsed/refractory large B-cell lymphomaRelapsed/ refractory B-cell precursor acute lymphoblastic leukaemia	2017 2018	US FDA EMA	
LUXTURNA (voretigene neparvovec-rzyl)	Adeno-associated viral vector–hRPE65	Spark Therapeutics	Biallelic RPE65 mutation–associated retinal dystrophy	2017 2018	US FDA EMA	
YESCARTA (axicabtagene ciloleucel)	Autologous CD19-CAR-T cells	Kite Pharma	Relapsed or refractory large B-cell lymphoma	2017 2018	US FDA EMA	

AAV, adeno-associated virus; ADA, adenosine deaminase; EMA, European Medicines Agency; EU, European Union; FDA, Food and Drug Administration; GTMP, Gene Therapy Medicinal Product; MA, Marketing Authorisation; SCID, severe combined immunodeficiency disease.
Zynteglo/*Autologous CD34+ cells encoding βA-T87Q-globin gene*/Bluebird bio/beta-Thalassemia/2019/EMA
ZOLGENSMA (onasemnogene abeparvovec-xioi)/Adeno-associated viral vector/AveXis, Inc/spinal muscular atrophy (SMA)/2019/FDA

Zynteglo in EU (EMA); Imlygic, YESCARTA, Kymriah, LUXTURNA, Zolgensma in the United States (FDA) (Table 11.1).

Since the first clinical trials of the 1990s, gene therapy has moved a long way from the investigational stage to being a part of evidence-based medicine, fulfilling the promises that were raised at its dawn.

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