CHAPTER 2

Development and Deployment of Gene Therapies: An ADA-SCID Case Study

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INTRODUCTION

Since the early 1970s, the knowledge that some diseases are genetically determined has inspired hope that targeted genetic changes might alleviate significant morbidity and mortality (Friedmann and Roblin, 1972). However, underlying disease complexity, technological challenges, and patient safety concerns have long forestalled the promised treatment revolution. The 2010s, however, have seen the first gene therapy (GT) approvals by the European Medicines Agency (EMA) (Glybera in 2012, Zalmoxis and Strimvelis in 2016) and the United States (US) Food and Drug Administration (FDA) (Kymriah, Yescarta and Luxturna in 2017; Zolgensma in 2019).

These approvals may well herald the long-promised arrival of personalised medicine, but they have also revealed technological, regulatory, commercialisation and access challenges. The unique trials and pathways required to bring an entirely new type of therapy to market require correspondingly innovative business practices. In this chapter, we present a broad history of GT, as well as a detailed discussion of the years-long cooperative efforts between GlaxoSmithKline (GSK) (Brentford, London, the United Kingdom (UK)) and The San Raffaele Telethon Institute for Gene Therapy (SR-Tiget) (Milan, Italy) that led to the development and approval of Strimvelis. These lessons learned not only serve as a model for future therapies but also suggest ways in which this exciting branch of medicine will continue to evolve.

HISTORY

GT is the intracellular delivery of foreign genomic materials into cells to treat or prevent disease by either correcting an existing abnormality or by providing cells with a new function (Nayerossadat et al., 2012; Ramamoorth and Narvekar, 2015; Thorne et al., 2016). The first step in GT development is understanding the underlying disease process and identifying the mutant gene responsible for the disease (Ramamoorth and Narvekar, 2015). This is then followed by cloning the therapeutic gene to replace, repair or regulate the nonfunctional sequence (Ramamoorth and Narvekar, 2015; Misra, 2013).

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Once prepared, the therapeutic gene (transgene) is loaded into or associated with a transporter (vector), which delivers it to target cells either in vitro (with subsequent reintroduction of target cells to the patient (ex vivo delivery)) or following injection directly into the patient (in vivo delivery) (Ramamoorth and Narvekar, 2015; Thorne et al., 2016) (Fig. 2.1). When the vector reaches the target cell, the genetic material may integrate into the deoxyribonucleic acid (DNA) and then correct or compensate for the defective or mutated gene. However, the decades that were required to approve the first GTs suggest that the biological reality is more complicated than this simplified schematic.

Early Development

In 1972, Friedmann and Roblin posed the question, 'Gene Therapy for Human Genetic Disease?', summarised genetic modification science to date and presented their vision of how GT might treat or prevent human diseases (Friedmann and Roblin, 1972). Their foundational work suggested future research in GT, predicted scientific problems and ethical issues and proposed preliminary criteria to guide GT in human patients. GT expanded with the development of viral vectors for stable integration of modified genes into target cells (Bouard et al., 2009). Development of GTs to treat primary immunodeficiency diseases (PIDs) started in the mid-1980s, using murine-based γ-retrovirus (γRV) vectors (Candotti, 2016). The first application of gene-modified haematopoietic cells in humans was reported in 1990, when retrovirus (RV)-mediated gene transduction

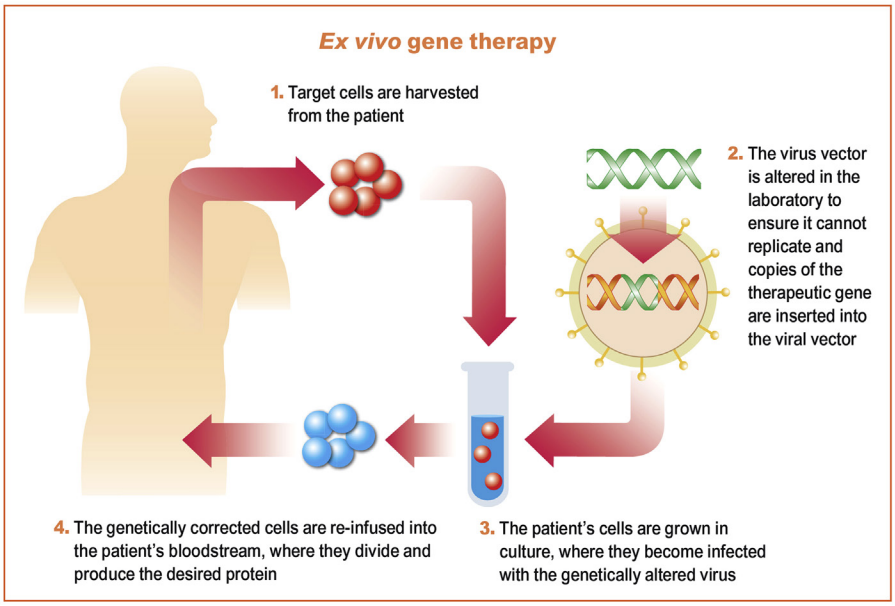

Figure 2.1 Ex vivo autologous gene therapy.

inserted a selectable marker gene into tumour-infiltrating lymphocytes (TILs) (Rosenberg et al., 1990). Persistence and localisation of TILs were then tracked after reinfusion into patients with advanced malignant melanoma (Rosenberg et al., 1990). Their results demonstrated the feasibility and safety of RV-transduced lymphocytes as a method of introducing genes into humans and suggested that RV vectors might be appropriate vehicles.

Vector Development

The most critical step in GT is vector selection (Ramamoorth and Narvekar, 2015); optimal vector-delivery system couples are determined by the target cells, duration of gene expression required and size of the genetic material (Kay et al., 2001; Ponder, 2001). Vectors must have a high safety margin, low toxicity, long-term stability and appropriate specificity (Bouard et al., 2009).

RVs, the first class of vectors used in preclinical studies and clinical trials (Collins and Thrasher, 2015; Keeler et al., 2017; Kotterman et al., 2015), naturally facilitate gene transfer into proliferating cells (including haematopoietic stem cells (HSCs)). Integration into the host cell chromatin is random and permanent (Kay et al., 2001;Vannucci et al., 2013). Other advantages include relatively large capacity, low immunogenicity, very low preexisting host immunity and wide cellular tropism (Vannucci et al., 2013). However, cells must be actively undergoing mitosis (division) for infection and transduction to occur, significantly limiting clinical application to select ex vivo targets (Kay et al., 2001). In addition, genotoxic events may occur, including insertional mutagenesis and oncogenesis resulting from random integration into the host genome (Ponder, 2001;Vannucci et al., 2013; David and Doherty, 2017). However, transduction stability is felt to compensate for potential genotoxicity, and RVs are still the preferred vector for ex vivo GT (Vannucci et al., 2013; Finer and Glorioso, 2017; Xu et al., 2017).

As with RVs, lentivirus (LV) integration into the host cell genome is stable and permanent (Kotterman et al., 2015). LVs also neutralise host cell defences, blunt the immune response and regulate viral replication. Importantly, LVs are able to integrate into both dividing and nondividing cells (Ponder, 2001; Vannucci et al., 2013). LV vectors were originally based on the human immunodeficiency virus 1 (HIV1) (Kay et al., 2001; Vannucci et al., 2013), leading to concerns about replication competent LV. The 3rd-generation self-inactivating (SIN) LV vector is considered safe and is currently the preferred tool for transferring genes into HSCs (Kotterman et al., 2015; Xu et al., 2017; Kaufmann et al., 2013).

Adenoviruses (ADVs) transduce both dividing and nondividing cells and exhibit low pathogenicity, high infectivity, natural delivery of the viral genome, high levels of transgene expression and no association with human tumours (Ponder, 2001;Vannucci et al., 2013). Unfortunately, ADVs are limited to transient transgene expression (Thorne et al., 2016;Vannucci et al., 2013), and broad preexisting immunity to circulating pathogenic

ADVs leads to tolerance. Organ inflammation and dysfunction can result from highly immunogenic proteins in adenovirus (ADV)-transduced cells (Ponder, 2001; Vannucci et al., 2013). Third-generation ADV vectors engineered to remove most viral genes have low immunogenicity, but manufacture is challenging (Thorne et al., 2016; Kay et al., 2001; Ponder, 2001; Kotterman et al., 2015; Alba et al., 2005).

Adeno-associated viruses (AAVs) are human parvoviruses whose replication requires either coinfection with a helper virus (e.g., ADV or herpes virus) or a genotoxic agent (Thorne et al., 2016; Ponder, 2001; Vannucci et al., 2013). Engineered AAV vectors remain predominantly in episomal form, are nonintegrating (Kay et al., 2001; Kaufmann et al., 2013) and have limited packaging capacity (Kay et al., 2001; Ponder, 2001; Finer and Glorioso, 2017). AAVs have wide cellular tropism and can transduce dividing and nondividing cells, with stable transgene expression in the absence of helper virus in postmitotic tissue (Ponder, 2001; Kotterman et al., 2015). New AAV vector subtypes circumvent the immune system and provide tissue specificity (Keeler et al., 2017), making these the preferred vectors for in vivo therapy of postmitotic tissues (Kotterman et al., 2015; Kaufmann et al., 2013; Maeder and Gersbach, 2016). The first GT treatment approved in a Western nation was an AAV1-based vector (Collins and Thrasher, 2015; Kotterman et al., 2015). A recent article by Schmid et al. reports on an emerging use of protein-engineered AAV in cancer therapy (Schmid et al., 2018). This new protein-engineered AAV increased tumour specificity while escaping liver and immune control (Schmid et al., 2018).

The Sendai virus (SeV) is a negative-sense, single-stranded ribonucleic acid (RNA) virus of the Paramyxoviridae family (Morodomi et al., 2013). The SeV offers a high efficiency of infection within minutes, a high level of gene expression and a low risk of pathogenicity to humans. A number of genetically modified and inactivated Sendai viruses have been characterised, with many of them offering unique anticancer mechanisms (Saga and Kaneda, 2015).

Nonviral vectors, including mechanical introduction, enhancement of cell membrane permeability and chemical methods, provide reduced immunogenicity or cytotoxicity compared to viral vectors, along with cost-effectiveness, availability and potential for transfer of relatively large (exact size ranges are not reported) DNA fragments into the host cell (Nayerossadat et al., 2012; Ramamoorth and Narvekar, 2015; Misra, 2013; Keeler et al., 2017).

Early ADA-SCID Gene Therapy

The first PID to be treated with GT was severe combined immunodeficiency (SCID) resulting from adenosine deaminase (ADA) deficiency (ADA-SCID) (Blaese et al., 1995; Bordignon et al., 1995; Hoogerbrugge et al., 1996; Kohn et al., 1995), an autosomal recessive metabolic defect that causes an accumulation of purine metabolites toxic to T, B and natural killer lymphocytes. Infants with ADA-SCID typically do not survive

beyond 1 year of age without effective treatment (Booth et al., 2016; Cicalese and Aiuti, 2015; Kuo and Kohn, 2016). ADA-SCID is a rare disease, with an overall incidence of 1 in 500,000 live births (Cicalese and Aiuti, 2015; Kuo and Kohn, 2016). Stem cell transplant from a human leukocyte antigen–matched sibling is the optimal treatment approach (Cicalese and Aiuti, 2015), although a suitable donor is often not available.

The first human GT trial took place in 1990 following a prolonged review by the National Institutes of Health and FDA (Blaese et al., 1995). Four-year-old Ashanti De Silva received multiple infusions of her own peripheral blood T lymphocytes that had been transduced with a human ADA gene-containing RV vector. Engraftment was successful, and immunological improvement occurred but did not allow discontinuation of enzyme replacement therapy (ERT) (Blaese et al., 1995).

In 1993, Andrew Gobea was the first infant to receive GT (Kohn et al., 1995). Umbilical cord blood was collected, isolated $CD34^+$ haematopoietic progenitors were transduced by *ada* complementary DNA in an RV vector and the gene-modified cells were reinfused on the patient's fourth day of life. The transgene persisted and was expressed for 18 months; this was associated with some normalisation of immune function, but supplemental ERT was again required. The early success stories of Ashanti De Silva and Andrew Gobea were well publicised and fostered public support of continued preclinical and clinical research in GT (Stolberg, 1993).

Early Gene Therapy Failures

In contrast to the clinical successes in early ADA-SCID GT trials, significant morbidity and mortality occurred in GT trials targeting other diseases. In 1999, 18-year-old Jesse Gelsinger was the first publicly identified patient to die in a GT trial, after the in vivo infusion of an ADV-derived vector triggered an intense inflammatory response and multiorgan failure resulting in death within 98 h (Steinbrook, 2008). Investigation revealed protocol violations, underreporting of adverse events and insufficient disclosure of potential conflicts of interest. As a result of Gelsinger's death, clinical trials specifically investigating GT fell under heavy scrutiny, with many ongoing trials at that time being immediately put on hold or cancelled (Gura, 2001). Furthermore, businesses were also significantly impacted, particularly in terms of investor confidence and the ability to attract additional financing. Many companies working on GTs either folded or began to focus their attention on other treatments (Bender, 2016). This series of events ultimately led to a significant decline in interest in GT research and a shift from ADV to AAV and LV vectors (Kotterman et al., 2015; Steinbrook, 2008; Schimmer and Breazzano, 2016a; Wilson, 2009).

Other GT trials were plagued by myelodysplasia and leukaemic transformation. Sixteen of 32 patients with X-linked SCID (X-SCID), Wiskott–Aldrich syndrome (WAS) or chronic granulomatous disease (CGD) treated with a first-generation γRV vector developed acute lymphocytic leukaemia (ALL), acute myeloblastic leukaemia

(AML), myelodysplastic syndrome or mutagenic clonal expansion (Xu et al., 2017; Booth et al., 2016; Cicalese and Aiuti, 2015; Kuo and Kohn, 2016; Fischer et al., 2015).

GT trials for X-SCID-utilising autologous $CD34^+$ cells transduced ex vivo with a murine γRV vector were begun in France in 1999 and in the UK in 2001 (Xu et al., 2017; Kuo and Kohn, 2016). In both trials, treatment resulted in stable reconstitution of cellular and humoural immunity; however, 5 patients developed T cell ALL due to the transactivation of protooncogenes. Sustained remission with retention of normal immunity was achieved with chemotherapy in 4 patients, but the fifth patient died despite chemotherapy and bone marrow transplantation (Xu et al., 2017; Booth et al., 2016; Cicalese and Aiuti, 2015; Kuo and Kohn, 2016).

The first clinical trial for WAS commenced in 2006 in Germany and included 10 patients treated with an infusion of autologous $CD34^+$ cells transduced with a WAS protein-expressing γRV vector (Xu et al., 2017; Booth et al., 2016; Cicalese and Aiuti, 2015; Kuo and Kohn, 2016). Nine of the 10 patients exhibited reconstitution of T cell function, antibody production, normalisation of platelet size and increase in numbers. However, aberrant expression of oncogenes induced by the integration of the γRV vector in proximity to the gene regulatory regions resulted in ALL and/or AML in seven patients; two patients died (Xu et al., 2017; Booth et al., 2016; Cicalese and Aiuti, 2015; Kuo and Kohn, 2016).

In 1995, a US trial using γRV vectors to treat CGD achieved short-term engraftment with no long-lasting benefit; one patient died of an invasive fungal infection. Other CGD GTs added preconditioning to a murine γRV vector; response to treatment improved but was incomplete and transient. One patient experienced a mutagenic clonal expansion but was successfully treated with HSC transplant; two adults and one child developed myelodysplastic syndrome due to insertional mutagenesis and died (Xu et al., 2017; Kaufmann et al., 2013; Cicalese and Aiuti, 2015).

It is unclear why no genotoxic events have been observed in ADA-SCID patients treated with the same vector system. It has been postulated that ADA deficiency itself may be unfavourable to leukaemogenesis (Cicalese and Aiuti, 2015; Fischer et al., 2015; Sokolic et al., 2011).

These early GT failures drove increased emphasis on vector design and development of SIN γRV and LV vectors. Early phase clinical trials using these vectors are in progress, and early results have suggested clinical efficacy and reduced insertional mutagenesis (Booth et al., 2016; Cicalese and Aiuti, 2015).

First Approvals

The first commercial GT, Gendicine, was approved in China in 2003 for head and neck squamous cell carcinoma via intratumoral injection (Table 2.1) (Ma et al., 2008; Pearson et al., 2004). Gendicine is a recombinant type 5 ADV expressing human wild-type *p53* gene (about half of human malignancies exhibit a loss of p53 functions, which are important to the maintenance of genetic stability) (Ma et al., 2008; Pearson et al., 2004).

Table 2.1 Summary of Worldwide Gene Therapy Approvals.

Product	Subtype	Indication	Approval Date and Country	Details
Viral				
Luxturna (voretigene neparvovec-rzyl)	AAV2	Biallelic RPE65 mutation-associated retinal dystrophy	2017 US	Retinal pigment epithelial cells with reduced or absent levels of biologically active RPE65 are transduced with a cDNA encoding normal human RPE65 protein
Kymriah (tisagenlecleucel-T)	LV	Relapsed or refractory ALL	2017 US	T cells are encoded with a CAR that identifies and eliminates CD19-expressing malignant cells
Yescarta (axicabtagene ciloleucel)	γRV	Relapsed or refractory large B-cell lymphoma	2017 US	T cells are encoded with a CAR that identifies and eliminates CD19-expressing malignant cells
Invossa (TissueGene-C)	MSCV RV	Osteoarthritis of the knee	2017 Korea	Allogeneic human cartilage cells transduced with an RV vector engineered to express transforming growth factor β1 (TGF-β1)
Strimvelis	γRV	ADA-SCID	2016 EU	$CD34^+$ cells are transduced ex vivo to express ADA then reinfused; $CD34^+$ cells engraft in bone marrow and repopulate the haematopoietic system
Zalmoxis	RV	Adjunctive treatment to haploidentical HSCT in adult leukaemia	2016 EU	Allogenic T cells transduced ex vivo with RV vector encoding for ΔLNGFR and HSV-TK Mut 2, given to control GvHD in haploidentical HSCT. EU approval conditional
Glybera (alipogene tiparvovec)	AAV1	Familial LPLD	2012 EU	Contains a human LPL gene variant. To be withdrawn from market effective October 2017
Gendicine	rADV5-p53	Head and neck cancer	2003 China	Vector expresses human wild type p53 promoting genetic stability missing in many tumour cells
Zolgensma (onasemnogene abeparvovec)	AAV9	Spinal Muscular Atrophy	2019 US	SMN protein production, required for survival of motor neurons, is promoted by administration of AAV9 virus capsids containing SMN1 transgenes
Nonviral				
Neovasculgen (PI-VEGF165)	Naked VEGF plasmid	Peripheral arterial disease	2011 Russia	VEGF promotes collateral circulation through stimulation of angiogenesis

AAV1 AAV2, or AAV9, adeno-associated virus type 1, type 2, or type 9; ADA-SCID, adenosine deaminase–deficient severe combined immunodeficiency syndrome; ADV, adenovirus; ALL, acute lymphocytic leukaemia; CAR, chimeric antigen receptor; cDNA, complementary deoxyribonucleic acid; EU, European Union; GvHD, graft versus host disease; HSV-TK Mut 2, herpes simplex 1 virus thymidine kinase; LPL, lipoprotein lipase; LPLD, lipoprotein lipase deficiency; LV, lentivirus; MSCV, murine stem cell virus expression system; rADV5, recombinant adenovirus type 5; RPE65, retinal pigment epithelial 65 kDa protein; RV, retrovirus; SMN, survival of motor neuron; US, United States; VEGF, vascular endothelial growth factor; γRV, gamma retrovirus; ΔLNGFR, truncated form of the human low affinity nerve growth factor receptor.
Based on Ma et al., 2008; Aiuti et al., 2017; EMA, 2012; Extance, 2015; Human Stem Cells Institute, 2011; Imlygic prescribing information, 2017; Kynamro prescribing information, 2016; Luxturna prescribing information, 2017; FDA, 2005; Novartis Pharmaceutical Corporation, 2017; Philippidis, 2017; Touchot and Flume, 2017; Yescarta, 2017; Zolgensma prescribing information, 2019.

Glybera (alipogene tiparvovec), an in vivo GT consisting of AAV1 carrying the human *lpl* gene, was the first GT to receive marketing authorisation from the EMA (EMA, 2017). It was approved in 2012 for the treatment of patients with lipoprotein lipase (LPL) deficiency, a rare condition with approximately 1 case per 1 million individuals (Cheever et al., 2015), who have severe or multiple pancreatitis attacks (EMA, 2012) (Table 2.1). Glybera is dosed according to body weight (EMA, 2017).

There were a number of setbacks in the approval process for Glybera primarily due to difficulties in demonstrating clinical benefit (Bryant et al., 2013). Following EMA authorisation, a retrospective analysis of 19 of 27 patients given Glybera revealed difficult-to-interpret findings relating to efficacy and benefit (Gaudet et al., 2016). While there was 50% reduction in pancreatitis events, there was also significant intra- and interpatient variability. At the time of launch in 2014, a course of treatment costs €900-1.1M (Touchot and Flume, 2017; Abou-El-Enein et al., 2016a). Due to the lack of recognition of benefit in individual European Union (EU) countries, extremely low postmarketing demand and high cost of manufacturing, the licence holder announced it would not apply for renewal of marketing authorisation, which effectively withdrew the drug from the market in 2017 (Touchot and Flume, 2017; Abou-El-Enein et al., 2016a; Hirschler, 2017a,b).

STRIMVELIS DEVELOPMENT

A key turning point in the treatment of ADA-SCID was the addition of nonmyeloablative busulfan conditioning prior to infusion of RV-transduced $CD34^+$ HSCs coupled with ERT cessation (increasing the survival advantage of gene-corrected HSCs) (Candotti, 2016; Aiuti et al., 2002). This approach lowered toxic purine metabolite levels, increased T cell counts, normalised T cell function and supported robust antigen-specific responses (Candotti, 2016; Aiuti et al., 2002).

It was this entire treatment protocol that the EMA approved in 2016 as Strimvelis (GSK2696273). The marketing application was supported by efficacy and safety data derived from 18 patients who were participants in pilot study 1 or 2 (Aiuti et al., 2002, 2009), a pivotal study (Aiuti et al., 2009; Cicalese et al., 2016) or a compassionate use program (CUP) (Cicalese et al., 2016; NICE Highly Specialised Technologies Evaluation Programme, 2017). The long-term follow-up (LTFU) component of the pivotal study followed all 18 patients over a median posttreatment period of 6.9 years (range: 2.3–13.4 years) (Cicalese et al., 2016).

Strategic Alliance

Fondazione Telethon (Telethon Foundation) is one of the largest biomedical charities in Italy, with a mission to advance biomedical research towards diagnosis, cure and prevention of genetic diseases (Ballabio and Naldini, 2015). SR-Tiget in Milan, which

pioneered the use of γRV-mediated GT in patients with ADA-SCID (Ballabio and Naldini, 2015), received financial support from the foundation.

In 2010, SR-Tiget and GSK entered into a strategic alliance for the development of GTs targeting ADA-SCID and six other rare genetic disorders including metachromatic leukodystrophy (MLD), WAS and CGD (Ballabio and Naldini, 2015; GSK, 2010; Mavilio, 2017). This alliance encouraged a collaborative approach to learning and developing GTs on a smaller scale for underserved patients with rare diseases; the foundational knowledge and experience gained by GSK from these efforts will also be beneficial in the event of expansion on a larger scale to additional cell-based therapies. As part of this strategic alliance, SR-Tiget conducted preclinical development and early clinical testing of new therapies based on LV vectors, whereas GSK developed ADA-SCID GT towards registration and commercialisation. GSK also acquired options for the treatment of the other six genetic diseases (Ballabio and Naldini, 2015; GSK, 2010; Mavilio, 2017; Wilson, 2016). The arrangement guaranteed that new GTs would be conceived and tested in a flexible academic environment but that they would be made commercially available by a partner with appropriate experience and resources (Mavilio, 2017; Wilson, 2016).

Strimvelis Efficacy

The relationship between SR-Tiget and GSK was preceded by proof-of-concept efficacy data from the 10 patients in the pivotal study (Schimmer and Breazzano, 2016a; Aiuti et al., 2009). In 2010, following formation of the alliance, GSK implemented a protocol amendment to the pivotal study that formally extended LTFU to more than 3 years and also enrolled patients from Pilot Study 2 and the CUP. The patient from Pilot Study 1 joined LTFU 13 years post-GT (NICE Highly Specialised Technologies Evaluation Programme, 2017). All 18 patients were alive in June 2017. ADA gene-modified cells have persisted long term, and ADA enzyme activity has increased. B-cell function has increased immunoglobulin production, produced antibody response to childhood vaccinations and decreased reliance on intravenous immunoglobulin. Severe infection rates declined from 1 year post-GT onwards. GT was considered unsuccessful by the company in three patients who required resumption of ERT. No insertional mutagenesis or oncogenesis has been observed among the 18 patients, an observation based on more than 130 patient-years of follow-up (Cicalese et al., 2016; Gennery, 2016).

Strimvelis Registry

Long-term efficacy and safety outcomes are monitored via the Strimvelis Patient Registry, a noninterventional, observational, prospective postauthorisation safety study (PASS) of patients up to 15 years posttreatment with Strimvelis (GSK, 2016a). The PASS will include all patients (target number is 50) treated with Strimvelis who consent to participation, including patients treated both prior to and following marketing authorisation.

The efficacy and safety data will be collected by the patients' local healthcare providers (Table 2.2) annually for the first 11 years after treatment and at years 13 and 15 thereafter (GSK, 2016a). Given that oncologic events in other programs were observed up to 6 years post-GT, the EMA Committee for Medicinal Products for Human Use agreed that a 15-year follow-up would be adequate to detect any potential oncologic signals (EMA Committee for Medicinal Products for Human Use, 2016). GSK will collect long-term events (i.e., oncogenesis, death, fertility and pregnancy outcomes) every 2 years until the registry is completely closed. After registry closure, patients or parents (or primary care physicians) will report any cancer event, death or adverse pregnancy outcome to GSK, whereon GSK will inform relevant authorities.

Table 2.2 Strimvelis Patient Registry Study Effectiveness and Safety Monitors.

Monitors	
Effectiveness Assessments • Survival • Intervention-free survival[a] • Use of medications/treatments of interest[b] • Immune reconstitution[c] • Growth[d] • Systemic metabolite detoxification[e] • Vector copy number[f] • Number and proportion of patients with severe infections[g] and associated hospital length of stay • Additional parameters reflecting the nonimmunological manifestations of ADA-SCID[i] • Paediatric development and quality of life data • Patient (or proxy) reported outcome measures and development questionnaires[j]	Safety Assessments • Frequency of adverse events and serious adverse events related to medical or surgical procedures associated with Strimvelis administration • Frequency of immune reactions • Frequency of oncogenesis • Frequency of reported adverse events and serious adverse events • Laboratory blood test results[h] • Fertility- and pregnancy-related outcomes • Data from RIS and RCR analysis

ADHD, attention deficit hyperactivity disorder; dAxP, deoxyadenosine nucleotides; ERT, enzyme replacement therapy; HSCT, haematopoietic stem cell transplant; PBMC, peripheral blood mononuclear cell; RBC, red blood cell; RCR, replication competent retrovirus; RIS, retroviral insertion site; TSH, thyroid-stimulating hormone; WHO, World Health Organization.

[a]Intervention is defined as HSCT or >3 months of ERT.

[b]ERT, HSCT, radiotherapy and cytotoxic agents.

[c]Absolute peripheral lymphocyte, absolute $CD3^+$ T cell and absolute $CD19^+$ B-cell counts and T cell function from response to mitogens.

[d]Height and weight percentiles as compared with WHO standard growth charts.

[e]Total dAxP levels in RBCs.

[f]Measured in PBMCs.

[g]Where severe infection is defined as an infection requiring hospitalisation or prolonging hospitalisation.

[h]i.e., biochemistry, haematology and TSH.

[i]i.e., hepatic steatosis, cognitive deficits, hearing impairment and behavioural abnormalities (including suspected or diagnosed ADHD or autism).

[j]Where used routinely as part of a physician's standard of care or where permitted by local authorities.

Based on GSK (2016a).

Success of Strimvelis

Vector Improvement

The first GT trials in ADA-SCID delivered the corrective *ada* gene to either T lymphocytes or cord blood/bone marrow progenitor cells using murine γRV vectors. Patients were not given busulfan preconditioning and were maintained on ERT posttreatment (Blaese et al., 1995; Bordignon et al., 1995; Hoogerbrugge et al., 1996; Kohn et al., 1995; Kuo and Kohn, 2016). Transduction rates were low, and ADA activity was insufficient to confer clinical benefit (Kuo and Kohn, 2016).

In subsequent trials, Moloney murine leukaemia virus–derived replication-deficient recombinant RVs were used to deliver *ada* (Kuo and Kohn, 2016). Ex vivo culture conditions improved transduction efficiency (Fischer et al., 2010; Mukherjee and Thrasher, 2013). Preconditioning with busulfan or melphalan improved engraftment of the infused corrected HSCs (Kuo and Kohn, 2016; Mukherjee and Thrasher, 2013). ERT was discontinued prior to GT, as a toxic metabolic environment might select for gene-modified progeny (Kuo and Kohn, 2016). These vector changes coupled with modifications in cell culture techniques and treatment protocol likely contributed to the high overall and intervention-free survival rates in subsequent trials (Cicalese et al., 2016).

Collaboration and Division of Expertise

Effective collaboration and sharing of expertise between SR-Tiget and GSK were crucial in the approval of Strimvelis. Based on the 2010 collaborative agreement, GSK provides the industrial skill necessary to design rigorous trials, develop scale-up manufacturing processes and analytical tests, track adverse events pre- and postmarketing, optimise the regulatory process and reduce product development costs (Ballabio and Naldini, 2015; Mavilio, 2017). SR-Tiget contributes a multidisciplinary research environment and access to good laboratory practice–compliant preclinical models, in addition to competence in conducting early phase clinical trials (Ballabio and Naldini, 2015). SR-Tiget chaperones GT programs to a prespecified proof of concept, when GSK can take on the program. To date, GSK has fully optioned GT treatments for WAS, MLD and beta-thalassaemia (in addition to ADA-SCID (Strimvelis)). This academic-industry collaboration has shown it can develop complex therapies for rare genetic diseases (defined as having prevalence rates ranging from ~4 to 6 per 10,000 individuals (Rudek and Korth-Bradley, 2016; Smith, 2016)) from concept to market in less than a decade (Mavilio, 2017).

In this partnership, it is imperative that there be open lines of communication, with ongoing joint steering committee meetings scheduled quarterly (additional ad hoc meetings, as needed). An Alliance Manager, the primary point of contact between the two groups, directs the flow of information, facilitates knowledge sharing and oversees a centralised data repository. A comprehensive collaboration agreement includes a well-defined scope of work and methods for conflict resolution, which should decrease disruptions due to differences of opinion. SR-Tiget has gained experience in the

requirements for the conduct of regulatory studies (preclinical and clinical) and in compliance with promotional activities and healthcare provider interactions. GSK has learned to interact with an academic group and better understand the complexities of developing a GT and guiding it through the regulatory approval process.

Treatment Manufacturing

An often underestimated factor in the development of GT is the manufacture of vectors and genetically modified cells (Mavilio, 2017). Researchers who develop innovative GT products and processes typically cannot scale those concepts into industrial methods that allow commercialisation at an acceptable manufacturing cost (Mavilio, 2017). MolMed S.p.A, a medical biotechnology company located within the San Raffaele Biomedical Science Park in Milan, was enlisted by GSK to develop the production process for Strimvelis. Manufacturing process optimisation, standardisation and characterisation were expanded from small-scale production to commercial supply (GSK, 2016b).

BUSINESS

During the commercialisation of Strimvelis, GSK advanced its corporate expertise in complex, highly specialised cell and GT treatments for underserved patients. GSK senior leadership acknowledged that the approval of Strimvelis would not necessarily generate profit for the company but was a first step towards a cell and GT platform. This was truly an innovative approach for a large pharmaceutical company and represented a sincere recognition of a new treatment paradigm. By leveraging the same technology platform across multiple indications, it should be possible to optimise development costs, resulting in increasingly cost-effective therapies. The recent decision by GSK to divest the Rare Disease GT portfolio is part of a shift in the strategic direction of the company. This decision will still allow GSK to leverage its learnings in the CGT field in collaboration with Adaptimmune towards the development of cell-based therapies such as Adaptimmune's TCR technology for larger oncology indications.

Given the rarity of ADA-SCID, GSK collaborated with payers to determine Strimvelis pricing that rewards innovation while delivering value to patients, clinicians and payers. To maximise availability, GSK will consider a variety of payment options. Based on the small number of expected patients, Strimvelis is currently reimbursed on a patient-by-patient basis in many EU countries. A reimbursement program in Italy was rapidly approved by the Italian Medicines Agency (AIFA), facilitating treatment for patients in Italy and via cross-border mechanisms. In October 2017, NICE recommended Strimvelis for use in selected UK patients in line with its indication, despite its high cost (£505,000) (NICE, 2017, 2018). GSK is committed to ensuring that candidates for treatment quickly and safely obtain appropriate care, which relies on a strong field medical team working with the referring medical team, both supported by commercial colleagues who can assist with defining options for financing therapy that promote access.

PAYMENT AND REIMBURSEMENT FOR CURATIVE TREATMENTS

The relatively short duration and small patient populations of GT clinical trials hinder the determination of the exact health and economic impact, leading to uncertainty in assessing the value of treatment. While GT is generally assumed to be curative, there are typically inadequate data to support long-term efficacy and safety. As a result, payers may be reluctant to price a one-time payment based on a projected lifetime of treatment effect (Abou-El-Enein et al., 2016a; Brennan and Wilson, 2014; Marsden et al., 2017; Schimmer and Breazzano, 2016b). Aside from the concerns over permanence of benefit and safety, there are additional issues to be considered in the determination of treatment value and pricing decisions for GT (Table 2.3) (Marsden et al., 2017).

GTs may also face significant marketing barriers if reimbursement is not thoughtfully structured, including the overall value of a potential cure, research and manufacturing costs and budgetary impact (Brennan and Wilson, 2014; Marsden et al., 2017; Schimmer and Breazzano, 2016b; Chen, 2017). While there is no established methodology to fully evaluate the value of a rare disease gene therapy, a number of funding models have been proposed that alter budgetary impact primarily by sharing risk between manufacturer and payer (Hanna et al., 2016; Lockhart and Hansen, 2016). Limits on the ability to assess

Table 2.3 Factors in Treatment Value and Cost of Drug.

Value of a Potential Cure
• Reduction of ongoing costs of patient support and management of chronic comorbidities
• Potential to end chronic treatments and thereby increase quality of life
Relevant Elements of Value
• Health gain for the patient
• Costs to the health system
• Societal willingness to pay for treatment based on disease severity or unmet need
• Societal prioritisation/willingness to pay for treatments for children over adults
• Potential for patient to increase productivity, return to work or study
• Reduction in burden of care to family members
High Research and Development, Approval and Production Costs
• Lengthy development and regulatory approval timelines
• Personalised nature of many gene therapies – scale and duration of manufacturing process
• Higher costs for clinical delivery when infrastructure changes are required
• Small patient numbers, manufacturers have fewer potential patients to recover R&D costs
• Limited life span or patent life of new therapies
Budgetary Impact
• Payers consider short time horizons in line with annual budgets, but impact of treatment may result in substantial savings over the patient's lifetime
• Aggregate number of patients within a healthcare system requiring a high-cost therapy may overwhelm financial resources

R&D, research and development.
Adapted from Marsden et al. (2017). Other references (Abou-El-Enein et al., 2016; Jackson and Naber, 2017).

GT durability or consistency have encouraged the development of annuity payment schemes, both with and without risk sharing (Abou-El-Enein et al., 2016a; Brennan and Wilson, 2014; Schimmer and Breazzano, 2016b). According to some plans, annuity payments may be made without reference to efficacy (Abou-El-Enein et al., 2016a) or, in performance-based plans, there is a one-time, up-front full payment or a stream of payments over the expected duration of benefit, with the permanence of either conditional on the technology delivering on its therapeutic claims (Abou-El-Enein et al., 2016a; Brennan and Wilson, 2014; Chen, 2017; Hanna et al., 2016). Italy is one of several countries within the EU that make frequent use of performance-based plans for innovative, high-cost therapies (Garrison et al., 2013; Navarria et al., 2015). In 2016, GSK agreed to a performance-based plan with the AIFA for Strimvelis (Regalado, 2016).

A 'flexible voucher' system has also been proposed, which would provide a GT manufacturer with patent extensions in return for their commitments to develop effective treatments for diseases with unmet needs and, once available, price those new treatments below certain limits (Schimmer and Breazzano, 2016b). Annuity and performance-based systems are simplest to implement when there is a single payer with which to negotiate and when there exists a single binary performance outcome (for example, successful vs. nonsuccessful) (Brennan and Wilson, 2014; Navarria et al., 2015). It is being anticipated that there will be a reduced potential for success of these payment plans in the US, where many payers exist and patients frequently switch insurance providers, making manufacturer–payer negotiations difficult (Brennan and Wilson, 2014; Schimmer and Breazzano, 2016b; Chen, 2017). However, the manufacturer of the first GT approved in the US (Novartis, Kymriah) has indicated that despite an established price of $475,000, it will create programs to allow insurers or government payers to forgo payment when patients do not respond to treatment within the first month and will reduce pricing for patients being treated for nonlabeled indications (Herper, 2017; Nisen, 2017; Novartis, 2017).

PERSPECTIVES

Limited Patient Population

Rare diseases are those diseases that affect a small number of people compared with other prevalent diseases (Rudek and Korth-Bradley, 2016). Importantly, however, there is no consistent worldwide definition for rare diseases; most definitions are limited to disease prevalence without consideration of disease severity (Rudek and Korth-Bradley, 2016; Smith, 2016). In the US and Japan, a rare disease is defined as one that affects <200,000 (~6 per 10,000) or <50,000 (~4 per 10,000) of each country's population, respectively. Alternately, the EMA defines rare diseases as those that are life threatening or chronically debilitating and affect no more than 5 in 10,000 people in the EU (Rudek and Korth-Bradley, 2016). Two major issues arise in the research and development (R&D) of therapeutic agents to alleviate rare diseases (most of which affect children and

are genetically determined): the difficulty in demonstrating a positive benefit–risk ratio when so few participants are available for study and the high cost of R&D relative to the size of the potential market (Smith, 2016; Cremers and Aronson, 2017; Henrard and Arickx, 2016).

The gold standard for clinical trial design is the double-blind, placebo-controlled, randomised controlled trial (RCT). However, this approach is impractical for a small patient cohort with a genetic disorder (Marsden et al., 2017; Cremers and Aronson, 2017; Gobburu and Pastoor, 2016; Kempf et al., 2017). It is difficult to recruit clinical trial participants when the pool of candidates is so limited; additionally, a small patient population may not be of adequate size to power an RCT, posing statistical challenges and a reduced ability to evaluate clinical efficacy and safety (Marsden et al., 2017; Cremers and Aronson, 2017; Gobburu and Pastoor, 2016; Philippidis, 2011). To gain the maximum insight into the GT being tested, all patients may need to receive active treatment (Marsden et al., 2017). Additionally, participants with a devastating disease may refuse a placebo when a potential treatment is available (Kempf et al., 2017). The geographic diversity of potential study participants and the limited GT treatment sites place a potentially significant travel burden on patients (Kempf et al., 2017). Accounting for small populations and related study issues, the EMA and FDA have provided scientific and regulatory guidance for approval of GTs (Tables 2.4 and 2.5) (Abou-El-Enein et al., 2015).

Future Research Funding

Due to their complexity, GTs incur high R&D and production costs (Marsden et al., 2017). If there was a validated methodology to determine the value of a GT treatment, adding R&D and production costs to that treatment value could reflect the maximum price society might pay for it; however, that price is not necessarily what should be paid (Marsden et al., 2017). While maximum pricing can generate return for investors and provide capital and incentive for future innovation, it can also reduce patient access to treatment or overwhelm healthcare budgets (Marsden et al., 2017; Abou-El-Enein et al., 2016b; Jackson and Naber, 2017). Some large manufacturers may choose to rely on other portfolio products with an established market share to provide overall financial success, with minimal revenues from innovative therapies (Abou-El-Enein et al., 2016b). Because large amounts of money are at stake, payers are questioning costs, reimbursement models, profit margins and returns, seeking a balance that will not only ensure fair returns to innovators but also affordability to payers (Marsden et al., 2017; Jackson and Naber, 2017).

There are a number of methods that can decrease the costs of R&D and production – indirectly promoting affordability – while incentivising GT development. Academia and charities play important roles in basic science R&D, which limits risk and reduces industry investment in the early development phases of a product (Mavilio, 2017).

Table 2.4 The European Medicines Agency and Gene Therapies.

Classification

The European Union (EU) classifies gene therapies (GTs), cell therapies and tissue engineering products as advanced therapy medicinal products (ATMPs) under Regulation (EC) No.1394/2007 and Directive 2001/83/EC.

Pathway

ATMPs are required to be assessed through the centralised authorisation procedure, via a single marketing authorisation application to EMA for all EU citizens at the same time.

ATMPs are the responsibility of the Committee for Advanced Therapies (CAT). The CAT is a multidisciplinary committee tasked with delivering recommendations on whether or not a medicine can be classified as an ATMP, as well as assessing the quality, safety and efficiency of ATMPs to produce recommendations on marketing authorisation. For GTs, there is also a Gene Therapy Working Party (GTWP) made up of people with expertise specific to GTs. The GTWP provides recommendations to the CAT on GT matters.

As with the FDA, the pathway for GTs is similar to that for other medicinal products but allows a tailored approach for individual ATMPs. There is an acknowledgement that large confirmatory studies may not be feasible due to small population sizes, and evaluation may need to be based on a limited amount of data. In addition, as with the FDA approach, all clinical studies are conducted in a relevant patient group rather than amongst healthy volunteers.

Companies developing ATMPs are eligible for reductions in the EMA fees (both for submissions and for scientific advice). Further incentives are available for products with an orphan designation, such as the possibility of obtaining 10 years of market exclusivity.

Guidance

Guidance documents that relate specifically to marketing authorisation applications of GTs are available on the EMA's website. One of the key documents is the EMA's draft guideline on the quality, nonclinical and clinical aspects of GT medicinal products (EMA/CAT/80183/2014). The document aims to provide guidance on the development and evaluation of GTs, focussing on quality (i.e., the specific requirement for development and manufacture) and the design of clinical and nonclinical study programs.

Gene Therapies to Date

Since 2009, the CAT has recommended that 170 products be classified as ATMPs; 31 of these are GTs; the rest are cell therapies or tissue engineering products. Of these GTs, only two have received market authorisation: Strimvelis and Glybera.

ATMP, advanced therapy medicinal products; CAT, Committee for Advanced Therapies; EMA, European Medicines Agency; EU, European Union; FDA, Food and Drug Administration; GT, gene therapy; GTWP, Gene Therapy Working Party.
Based on www.ema.europa.eu; (Salmikangas et al., 2015); source for text box ICER, 2017 White Paper (Marsden et al., 2017).

Governments have introduced legislation and regulations that encourage the development of GTs and other rare disease treatments, due to concerns that development was discouraged by the cost of research and anticipated limited return on investment (Cremers and Aronson, 2017; Haffner, 2016). Programs vary, but they can include tax credits and research aids, grant programs and protocol assistance for clinical drug development, simplification of marketing authorisation procedures, exemption from fees and

Table 2.5 The Food and Drug Administration and Gene Therapies.

Classification

The FDA refers to gene therapies (GTs) as human GT products. They are often considered alongside cell therapies, collectively referred to as 'Cellular and Gene Therapy Products'. The majority are biologics, although some may be medical devices or combination products.

Pathway

The Office of Tissue and Advanced Therapies (OTAT), formerly the Office of Cellular, Tissue and Gene Therapies (OCTGT), and part of the Center for Biologics Evaluation and Research (CBER), regulates GTs alongside cell therapy products and related devices. CBER provides management and support to the Cellular, Tissue and Gene Therapies Advisory Committee, which reviews and evaluates data relating to the safety, effectiveness and appropriate use of these products.

The regulatory approach for GTs is similar to other medical products but does include flexibility related to the biological and technical complexity of the products. For example, phase I studies for GTs are typically conducted in a population that has the disease being studied (rather than in healthy volunteers). This is mainly due to unknown risks, but it also allows sponsors to look for preliminary evidence of bioactivity on the characteristics of the disease.

GTs may also be able to achieve orphan status (which qualifies manufacturers for benefits such as tax credits) and/or be eligible for one of the four available mechanisms for expediting FDA assessment: breakthrough designation, fast-track designation, accelerated approval or priority review.

Guidance

There are several guidance documents available on the FDA website to support manufacturers in developing, reporting on and conducting studies of cell and GT products. Key documents include

- Considerations for the design of early-phase clinical trials of cellular and gene therapy products; guidance for industry
- Guidance for industry: gene therapy clinical trials – observing subjects for delayed adverse events
- Recommendations for microbial vectors used for gene therapy; guidance for industry CBER is also able to provide early scientific and regulatory advice.

Gene Therapies to Date

There have been GTs that have achieved orphan drug designations (for example, Agilis' AGIL-FA for the treatment of Friedreich's ataxia and Spark Therapeutics' voretigene neparvovec for the treatment of inherited retinal dystrophy due to biallelic rpe65 mutations) and been eligible for expedited development and review. Voretigene neparvovec and Spark/Pfizer's SPK-9001 (for the treatment of hemophilia B) have both achieved breakthrough designation.

CBER, Center for Biologics Evaluation and Research; FDA, Food and Drug Administration; GT, gene therapy; OCTGT, Office of Cellular, Tissue and Gene Therapies; OTAT, Office of Tissue and Advanced Therapeutics.
Based on www.fda.gov; (Bailey et al., 2015); source for text box ICER, 2017 White paper (Marsden et al., 2017).

extended market exclusivity (Abou-El-Enein et al., 2016a; Cremers and Aronson, 2017; Henrard and Arickx, 2016; Haffner, 2016) (Tables 2.4 and 2.5). Some pharmaceutical manufacturers, including GSK, have created orphan drug or rare disease units to maximise in-licencing opportunities and utilise development and regulatory expertise in the most efficient manner (Philippidis, 2011).

Technology

New technology will be required as GT matures and evolves towards difficult-to-treat disorders. Future challenges will require design of safer vectors, incorporation of regulatory elements to improve clinical efficacy, optimisation of cell culture methods to preserve viability and function during manufacture, incorporation of patient pretreatment conditioning and development of gene-editing methodologies (Kotterman et al., 2015; Thrasher and Williams, 2017).

Despite the successful use of viral vectors in clinical trials, challenges persist, including manufacturing limitations, immunogenicity, less than optimal transport and infectivity of target cells, risk of oncogenesis and maintenance of high and stable transgene expression (Kotterman et al., 2015; Kuo and Kohn, 2016; Wirth et al., 2013). Next-generation vectors have been engineered that evade the immune system, enable tissue-specific tropism and are less likely to cause insertional mutagenesis (Keeler et al., 2017; Rivat et al., 2012). SIN γRV or SIN LV vectors, for example, show high efficiency in sustainable transgene expression and reduce risk of insertional mutagenesis in vitro and in vivo (Cicalese and Aiuti, 2015). There will also be advances in the use of nonviral DNA vectors to decrease cellular toxicity, increase transfection efficiency, facilitate payload delivery, enhance purity and yield and decrease expense (Hardee et al., 2017). In addition to vector engineering, enhancement of the genetic material may improve GT efficacy and safety. For example, the use of cell-type specific promoters instead of strong viral promoters may reduce the risk of endogenous gene activation and potentially limit transcription to the cell or tissue of interest (Kotterman et al., 2015).

Viral vector–mediated methods of GT result in random delivery and incorporation of functional genes, without targeting their natural location in the genome; this insertion of an exogenous DNA copy into a target cell genome raises the potential for genotoxicity (Kuo and Kohn, 2016; Xiao-Jie et al., 2015). Recently, there has been increased emphasis on site-specific GT, and technological advances have created gene-targeting approaches based on artificial endonucleases. Zinc finger nucleases, transcription activator-like effector nucleases and clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9) RNA-guided nucleases have particular promise (Booth et al., 2016; Cicalese and Aiuti, 2015; Kuo and Kohn, 2016). These methods permit the inactivation of target genes, or insertion of therapeutic genes into the genome, without the use of integrating viral vectors, thereby potentially decreasing the risk of insertional oncogenesis or ectopic protein expression (Xu et al., 2017; Cicalese and Aiuti, 2015; Kuo and Kohn, 2016). There are continued research challenges

with these gene-editing platforms; however, their ability to cure disease has been demonstrated both by in vitro and animal models, and further refinement of the technology will likely lead to a significant role in GT (Candotti, 2016; Booth et al., 2016; Kuo and Kohn, 2016; Komaroff, 2017).

Clinical experience to date with busulfan conditioning has indicated that it is generally well tolerated; however, concern for potential toxicities and delayed immune reconstitution has generated interest in alternative strategies such as selective depletion of blood cells in bone marrow using monoclonal antibodies (Thrasher and Williams, 2017; Bernardo and Aiuti, 2016). Another important development will be the capability to efficiently freeze, thaw and expand stem cells. This can reduce geographical barriers and improve patient access to GT by centralising resources and expertise for stem cell manipulation and gene delivery and by promoting an environment conducive to new trials in GT (Candotti, 2016; Xu et al., 2017; Abou-El-Enein et al., 2016a).

In conclusion, the development of safe and effective GTs has been a multidecade effort (Fig. 2.2) with more than a few false starts and dead ends, and it has been nothing short of

Figure 2.2 Major events in clinical gene therapy. *(Based on Keeler et al. (2017), Kaufmann et al. (2013), Aiuti et al. (2017), Bryant et al. (2013), Thrasher and Williams (2017) and Wirth et al. (2013).)*

revolutionary for both the scientific and medical communities. It is unsurprising, then, that the regulatory and business communities have likewise developed unique and innovative frameworks for this new field. Advances in viral design and understanding of underlying disease pathology will continue to drive development of novel GTs, but parallel breakthroughs in trial design, research collaborations and pricing structures will be responsible for turning those scientific discoveries into marketable products available to patients.

ABBREVIATIONS

AAV Adeno-associated virus
ADA Adenosine deaminase
ADA-SCID Adenosine deaminase–deficient severe combined immunodeficiency
ADHD Attention deficit and hyperactivity disorder
ADV Adenovirus
AIFA Italian Medicines Agency
ALL Acute lymphocytic leukaemia
AML Acute myelogenous leukemia
ATMP Advanced therapy medicinal product
CAR Chimeric antigen receptor
CAT Center for Advanced Therapies
CBER Center for Biologics Evaluation and Research
CGD Chronic granulomatous disease
CRISPR Clustered regularly interspaced short palindromic repeats
CUP Compassionate use program
dAxP Deoxyadenosine nucleotides
DNA Deoxyribonucleic acid
EMA European Medicines Agency
ERT Enzyme replacement therapy
EU European Union
FDA Food and Drug Administration
GSK GlaxoSmithKline
GT Gene therapy
GTWP Gene Therapy Working Party
HIV1 Human immunodeficiency virus 1
HSC Haematopoietic stem cell
HSCT Haematopoietic stem cell transplant
LPL Lipoprotein lipase
LPLD Lipoprotein lipase deficiency
LTFU Long-term follow-up
LV Lentivirus
MLD Metachromatic leukodystrophy
MSCV Murine stem cell virus expression system
OCTGT Office of Cellular, Tissue and Gene Therapies
OTAT Office of Tissue and Advanced Therapies
PASS Postauthorisation safety study
PBMC Peripheral blood mononuclear cell

PID Primary immunodeficiency disease
R&D Research and development
rADV5 Recombinant adenovirus type 5
RBC Red blood cell
RCR Replication competent retrovirus
RCT Randomised controlled trial
RIS Retroviral insertion site
RNA Ribonucleic acid
RV Retrovirus
SCID Severe combined immunodeficiency
SIN Self-inactivating
SR-Tiget The San Raffaele Telethon Institute for Gene Therapy
TIL Tumour-infiltrating lymphocyte
TSH Thyroid-stimulating hormone
UK United Kingdom
US United States
VEGF Vascular endothelial growth factor
WAS Wiskott–Aldrich syndrome
WHO World Health Organization
X-SCID X-linked severe combined immunodeficiency
γRV γ-Retrovirus

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