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Review Article

Cell and Gene Therapy in Cancer

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ABSTRACT

At various points throughout the life cycle of a pharmaceutical product, analytical procedures must be established. If these tasks are not appropriately simplified based on scientific knowledge and process understanding, it could result in an extremely expensive and time-consuming approach. The pharmaceutical industry is constantly looking for new guidelines or components to add to or replace the current components of the quality and risk management system The idea of Quality by Design was first introduced by renowned quality expert Joseph M. Juran. (QbD). Analytical method development, or AQbD, can be thought of as an extension of QbD. A methodical approach to development known as "Quality by Design" starts with predetermined objects and places a strong emphasis on process control, product and process understanding, and understanding .contemporary method approach The current review article's primary goal is to outline the various QbD processes while also addressing implementation-related issues. ATP (Analytical Target Profile), CP (Performance Attributes), MODR (Method Operable Design Region), Control Strategy, and Continual Method Improvement are all included in the creation of an analytical method

INTRODUCTION

Over eight million people worldwide lose their lives to cancer each year, making it a serious global health concern. The disease is intricate and multifaceted, involving alterations in the DNA that are coordinated by interactions between the environment and the host [1]. The ability to invade and spread across tissues, self-sufficiency in growth signals, insensitivity to anti-growth signals, limitless capacity for reproduction, persistent angiogenesis, and evasion of apoptosis are characteristics of cancer [1]. A key factor in the development and spread of tumors is the extracellular matrix and the tumor microenvironment, which are made up of different non-malignant cells that express different regulatory proteins [2]. Target cell expression of genetic material is the aim of gene therapy in order

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to achieve a therapeutic effect. Its ability to be applied locally, where a high therapeutic dose can be delivered without taking the risk of experiencing systemic negative effects, gives it an advantage over traditional therapies. Moreover, given that the majority of gene therapies are one-time treatments, they may end up being less expensive over time. An Overview of Cancer Gene Therapy Rogers et al. were among the first to provide a preliminary proof-of-concept for virus-mediated gene transfer. He showed how viruses can be used to insert foreign genetic material into cells that are of interest [3]. Inspired by the outcomes, he conducted more testing on human subjects. Rogers carried out the first human gene therapy study using this experiment. In that investigation, Rogers intended to transfer the arginase gene into two girls who had hyper argininemias, urea cycle disorders, using a wild-type Shope papilloma virus [4,5]. He postulated that the gene encoding arginase activity would be naturally encoded by the Shope papilloma virus and that the patients could get the virus and pass on this gene. Regretfully, the trial resulted in a bad consequence. Both the clinical course of the disease in these patients and their arginine levels remained unchanged. Rogers "out of the box" thinking was intriguing, but it was bound to fail when it was discovered that the arginase gene is not encoded in the genome of the Shope papilloma virus. The first gene treatment regimen was approved by the US Food and Drug Administration (FDA) and implemented in 1989. Tumor infiltrating lymphocytes were obtained from patients with advanced melanoma, grown in vitro, and then reinfused into the patients after being transduced ex vivo, using a marker gene that isn't a therapeutic gene [6]. The next year saw the initiation of the first clinical trial on cancer with a therapeutic aim, treating patients with metastatic melanoma using tumor infiltrating lymphocytes that had been genetically engineered ex vivo to express tumor necrosis factor [6]. Another significant turning point in the history of gene therapy was the work carried out by Cline et al. The patients received their cells back after they had been transfected [7, 8]. The trial was conducted without the University of California, Los Angeles (UCLA) Institutional Review Board's approval, which is why it represents a turning point in the gene therapy's past rather than the study's inherent failure. This instance showed how little was known and how much more difficult human gene therapy would be on both a technical and moral level than anticipated.

Methods of Gene Transfer and Vectors Employed in Gene Therapy:

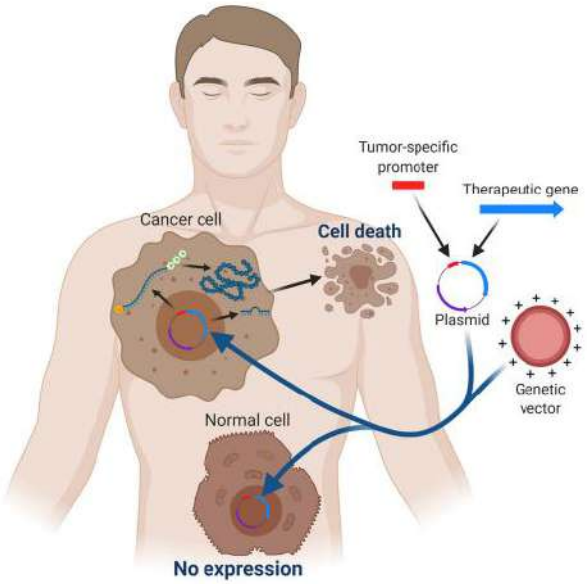

Figure 1: Gene therapies for cancer treatment

The hurdles in gene therapy are delivering a suitable amount of genetic material into target cells or tissues and maintaining gene expression for the desired duration. Genetic material can be injected into target cells or tissues using a variety of delivery techniques. They can be classified as physical, viral, non-viral, or bacterial or yeast, according to theory. Physical methods such as electroporation, ultrasound, and gene gun delivery have been used. As the name implies, genetic material can be transferred into cells using synthetic carriers like liposomes or nanoparticles

in non-viral gene transfer techniques, whereas biological, or virus, vectors are used in viral vector techniques. Different vectors show different traits with respect to their transduction effectiveness and ability to efficiently express the injected genes. They also differ in terms of the transgenes' safety profile and expression duration. Depending on the needs, different vectors can be used for various therapeutic purposes. Currently, the most effective gene delivery method for in vivo gene transfer is believed to be viral vectors. The perfect gene transfer vector should be able to transducely target a specific tissue and sustain stable, regulated gene expression without inducing immunogenic responses or other unfavorable outcomes. Unfortunately, none of the gene delivery vectors now in use fulfill all of these specifications. The effect region is typically exact but limited when a vector is injected locally. On the other hand, a system-wide expression could result via systemic vector delivery. Consequently, vectors and the ways in which they are administered have been modified in order to increase transduction efficiency and achieve targeted dispersion, as seen in figure 1 [9,10].

Viral Vectors:

Adenoviruses, lentiviruses, retroviruses, adeno associated viruses are the viral vectors for gene transfer that are most commonly used. The cell tropisms, expression profiles, transgene capabilities, immunogenicity, and longevity of transgene expression of these vectors vary from one another. Viral vectors can be separated into integrating and non-integrating vectors in addition to their origin. Conversely, lentiviruses, retroviruses are examples of vectors that actually assimilate into the DNA of the host. When using non-integrating viral vectors, the transgene's expression is temporary and fades within a few weeks, but when using integrating vectors, the expression typically lasts for months or even years. The safety of these vectors has come under scrutiny due to the transgene integration with the host's DNA. This is because integration has occasionally been seen to occur at actively expressed regions (i.e., insertional mutagenesis) when using retroviral vectors [11–13].

Another method for delivering genetic material is ex vivo gene transfer. In this procedure, genetic material is given to autologous cells that have been previously extracted and then reintroduced to the patient a process known as ex vivo. As of right now, adenoviruses dominate the gene delivery vector market for gene therapy as shown in table 1. Adeno viruses have been found to contain over 50 distinct serotypes, which are further separated into six subgroups (A–F) [14]. The most often utilized serotypes in gene therapy are those 2 and 5. One of the constraints associated with adenoviruses. Which could potentially affect transduction efficiency and treatment efficacy. It has been demonstrated that viral vectors are effective gene transfer agents. However, disadvantages including the ability of viral vectors to cause inflammation and immunostimulation, as well as their quick excretion from the bloodstream, have pushed for the creation of novel synthetic gene delivery vectors. As an alternative to viral delivery systems, non-viral gene delivery systems are actually a subject that is being thoroughly researched right now. Naked plasmid DNA is the most basic type of non-viral system available. The benefit of using a naked plasmid is that there is minimal risk of toxicity or unintended reactions. It is also inexpensive to make and simple to formulate. Its low transfection efficacy in comparison to viral-mediated gene transfer is a drawback, albeit [15]. Therefore, in order to protect DNA degradation and increase plasmid uptake and transfection, formulations including cationic polymers or lipids have been created to condense plasmid DNA and improve transfection efficiency [15]. The benefit of those formulations is that certain qualities can be fairly simply

engineered into polymers or lipids. For instance, by attaching cell- or tissue-specific targeting moieties on the carrier, non-viral vectors can be readily directed to a particular tissue or cell. The biodistribution, cellular internalization, and intracellular trafficking of the micro- or nanoparticle can also be affected by the size of the particle [16]. Regrettably, non-viral delivery techniques have not shown much success in clinical gene therapy applications. Non-viral vectors have not undergone the same evolutionary process as viruses, which is often reflected in their low in vivo transduction efficiency. The success of non-viral gene therapy depends on the several extracellular and intracellular barriers that affect the efficacy of all gene delivery methods, including cellular absorption, endosomal escape, nuclear uptake, and gene expression [16–18].

Cancer Specific Gene Therapy:

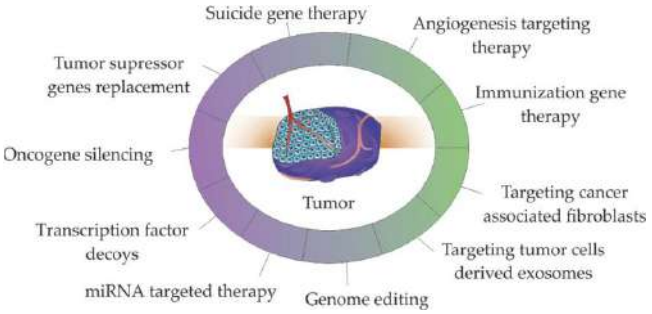

Figure 2: key strategies in the treatment of cancer using non-viral gene therapies.

Tumor suppressor gene expression can be restored or oncogenes silenced by delivering TNAs, such as genes, oligonucleotides, miRNAs, or siRNAs, to cancer cells [19–20]. The majority of these methods such as gene editing, RNA interference (RNAi), and antisense therapy aim to modify or alter genes [20–23]. Immunization gene treatments, in particular those based on chimeric antigen receptor in T cells (CAR-T cells), are noteworthy because they account for a greater proportion of therapeutic approaches used in clinical practice [24–29]. It should be mentioned that some of the tactics discussed as shown in figure 2, including genome editing or targeted therapy with miRNA or siRNA, are utilized to target TMEs via immunological treatments and angiogenesis [30-32].

RNAi-Based Oncogene Silencing

Delivering nucleic acids that enable specific genes to be downregulated into tumor cells is known as gene silencing [33-34]. The aim for a particular mRNA's complementary sequence of a selected gene, either by preventing protein synthesis or by promoting its destruction, gene silencing therapy is typically carried out by introducing siRNA or shRNA into tumor cells [35]. Genes implicated in the resistance to drugs, including MDR1 and oncogenes, like, cMYC or KRAS, are attractive targets for RNA interference (RNAi) tumor therapy [36]. RNAi encounters several significant obstacles, including target selectivity, off-target RNAi action, circulation dissipation, cellular internalization, and endosomal escape [37].

Replacement of Tumor Suppressor Genes

Gene transduction, preserving the steadiness and complete gene expression or restoring gene mutations are the three methods available for replacing lost genes (reviewed in [96]). Major candidates for gene substitution therapy include tumor suppressor genes like TP53, P21, and PTEN [38-40]. The TP53 gene is a primary target for gene therapy because of the pivotal function that the P53 protein plays in the regulation of the cell cycle, DNA repair, apoptosis, senescence, and/or autophagy [41,42]. Since transverse RNA delivery constraints in gene editing also affect DNA delivery, it is necessary to get over the obstacle of nucleus membrane crossing [43]. Short kilobase pair (kbp) cassettes expressing therapeutic genes may find it difficult to nuclearly enter the nucleus. Which permit linear DNA with maximal lengths of 200–300 bp [44]. Nucleotide sequences included in DNA or localization of nuclear markers are two methods to enhance DNA entry into the nucleus. The previously mentioned strategies are limited in their application for cancer therapeutics because

they require the activation of signaling pathways. A recent assessment of the obstacles and approaches of nucleic acid delivery-based gene editing was published in [44].

Targeted Therapy with microRNAs

Certain miRNAs are overexpressed in cancer, leading to the development of tumors (oncomirs); other miRNAs, known as tumor suppressor miRNAs, regulation of cell death [45]. Repositioning the amounts of miRNAs in cells is the goal of miRNA targeted therapy. Although the miRNA's mechanism of silence is comparable to that of RNAi, Complementary or semi-complementary sequences make up miRNA that are located either in the 30 -UTR of a particular mRNA target or in many mRNAs that are implicated in a specific cellular function [20,46]. Using miRNA-duplexes, siRNA complementary to the seed sequence of the miRNA of interest, or under expressed miRNA [47]. Many studies suggested rearranging miRNAs to facilitate cancer therapy. For instance, miRNA Let-7c, a tumor suppressor, could be added to treat prostate cancer, miR-21 in breast cancer could be silenced [48, 49]. Possible side effects, toxicity caused by miRNA, and degradation of single- or double-stranded miRNA in the endosome or circulatory system, and inadequate delivery have all presented challenges to the therapeutic systemic delivery of free miRNAs [50,51]. Understanding how miRNAs affect the metabolism of both cells is crucial for preventing off-target effects, which can arise from partial complementarity with non-targeted transcripts or from causing undesirable consequences through the control of non-targeted cells' metabolic activities [51]. MiRNA can be altered to get beyond the restrictions on destruction. The passenger strand methylation of miRNA mimics and the use of locked nucleic acid (LNA) chemistry to alter anti-miRNA are the two basic methods of modification [50].

Transcription Factor Decoys (TFD)

Double stranded oligodeoxynucleotides (ODN) called TFD are intended to block particular regulatory circuits [52]. The transcription factor consensus DNA recognition motif or the sequence of a certain genes transcription factor is included in TFD-ODNs, which are short double-stranded DNA molecules that compete with certain transcription factor binding sites [53]. Two of the biggest obstacles to using TFD-ODNs in cancer treatment are the design of the TFDs and their stability in the endosome and circulatory system [54]. The precise transcription factor binding site sequence is necessary for the design of TFDs, but this can be difficult to achieve due to discrepancies in database data. Therefore, expensive and time-consuming methods like chromatin immunoprecipitation must be used, as well as additional confirmation of accurate targeting typically through the use of scrambled decoys and reporter genes like luciferase. Chemical modifications of the TFD-ODNs with phosphorotioate (PS), lignin (LNA), or peptide nucleic acid (PNA) could boost their resistance to serum nucleases, lower their half-life, and improve their interaction with DNA binding proteins. However, their nanoparticle transport is one of the most promising methods for TFD-ODN distribution in vivo [54, 55].

Genome Editing

The process of modifying intracellular DNA via insertion, deletion, integration, or sequence substitution is known as genome editing therapy [55,56]. The selectivity of the Cleavage of DNA and the avoidance of unintentional damage to the remaining genome are key factors in the effectiveness of the genome editing therapy. It has been demonstrated that the CRISPR/Cas9 system is an effective and stable method for editing genomes and for high-throughput screening for mutations linked to tumor development and oncogenesis [57,58]. The CRISPR system of Streptococcus pyogenes (SpCas9) is the most

widely used CRISPR/Cas9 system. It recognizes the short sequence 50 -NGG, where N is any nucleotide and G is guanine. Cas9 is a nuclease that is guided by a single guide RNA (sgRNA) that is mediated by paring to the target region. Delivery methods for the CRISPR/Cas9 system include plasmids and linear DNA encoding sgRNA and Cas9 [59, 60]. While plasmid DNA allows for stable and long-lasting gene expression, supplied linear DNA must enter the nucleus for transcription [59]. Furthermore, extended exposure of the genome to endonuclease activity, which causes the cleavage of off-target sites, is a problem for genome editing based on this method [59, 60]. To prevent off-target mutagenesis, the CRISPR/Cas9 system expression in non-target tissues should be reduced [59].

Suicide Genes

Suicide gene therapy was first suggested as a means of treating cancer. consist of using two primary techniques to introduce a gene producing a cytotoxic protein into tumor cells: Two methods of gene therapy are available: (i) direct gene therapy, which involves inserting a toxin gene into tumor cells to decrease their viability, and (ii) indirect gene therapy, which involves inserting an enzyme gene into tumor cells to transform a non-toxic prodrug into a cytotoxic drug [61,62]. In 1983, the first suggestion for suicide gene therapy was made, which involved introducing the herpes virus thymidine kinase gene into BALB/c murine cell lines and using these cells to produce tumors in BALB/c animals [63]. The animals were subsequently given ganciclovir (9-([2-hydroxymethyl) ethoxy] methyl) guanine), and tumor regression occurred as a result of ganciclovir's metabolization by herpes virus thymidine kinase at the tumor cells [63, 64]. This therapy approach promise led to its use in other clinical trials, such as those treating colorectal (NCT00012155) and liver (NCT02202564) cancers. The problems with suicide gene therapy stem from the requirement for gene editing to produce high gene expression in tumors, preferably under the control of tumor-specific promoters [65].

Gene Therapy for Immunizations

Enhancing the immune system ability to combat TME cells primarily tumor cells is the goal of immunization gene therapy. Cytokine gene therapy, tumor vaccine therapy, and CAR-T cell therapy are the three main strategies used.

Vaccines against tumors

The mechanism of tumor vaccination is to expose the immune system to antigens related to tumors, which in turn stimulates an immune response against antigens or indicators of cancer [62]. Prostate-specific antigen (PSA), differentiation antigens like glycoprotein 100, and tumor-specific epitopes are examples of proteins that are overexpressed in cancer cells and are considered tumor-related antigens [63, 64]. Tumor-specific epitopes, or neoepitopes, are created when protein sequences are altered by genomic instability in tumor cells and are identified by T lymphocytes. With the development of Next Generation Sequencing (NGS), it is now possible to forecast neoepitopes for customized cancer therapy and get a thorough mapping of the mutations present in a particular tumor [65]. One way to achieve this is by administering a neoepitope vaccination to the patient, which will activate their immune system to fight tumor cells. Synthetic peptides, mRNA, pDNA, viral vectors, engineered attenuated bacterial vectors, and genetically modified APCs, such as activated B cells, macrophages, and dendritic cells (DCs), are examples of vectors for neoepitope presentation. The FDA has approved Sipuleucel-T (Provenge, Dendreon Corporation), a DCs-based vaccine, to treat castrate-resistant prostate cancer [66]. DCs have emerged as the most promising immunization vectors. The complexity of tumor points mutations, however,

makes it difficult to identify a neoepitope that can effectively trigger an immune response [67,68].

Therapy using CAR-T Cells

Tumor vaccine therapy and CAR-T cell therapy follow similar strategies. This method involves genetically modifying T cells taken from a donor who is in good health or from a patient to create antigens against neoepitopes before reintroducing the cells to the patient [69]. Two main factors are impeding the widespread use of CAR-T cell therapies for tumor treatment: the target miss effect, which arises when target antigens are not highly expressed in tumor cells or present in normal cells; and the over-activation of the immune system, which can lead to T-cell death and excessive production of cytokines, which can cause nausea, fatigue, anorexia, and high fever [69]. Though two CAR-T cell-based viral therapies tisagenlecleucel (Kymriah, Novartis) and axicabtagene ciloleucel (Yescarta, Gilead)—have been approved by the European Commission for the treatment of hematological neoplasms, the therapeutic approach utilizing CAR-T cells has shown promising results for the treatment of aggressive B-lymphoma and B-cell precursor acute lymphoblastic leukemia [70]. The scientific community is enthusiastic about it, but its widespread application is limited by the related expenses (discussed in [28,128]). The requirement for large-scale viral vector production and related quality control carried out by highly skilled personnel represents another constraint [71]. Non-viral approaches, such as pDNA transfection, various nano formulations, and transposon-based vectors like Sleeping Beauty and PiggyBac [72], are being investigated in an effort to get over these barriers [73,74].

Genes for Cytokines

Increased levels of cytokines with anti-tumor properties, such as interleukin-2 (IL-2), IL-4, IL-6, IL-12, IL-24, interferon-alpha (IFN-α), IFN-γ, IFN-β, or tumor necrosis factors (TNF) TNF-α and TNF-β, are essential for the basic principles of cytokine gene therapy. Innate and adaptive immune responses are subsequently triggered by the engagement of IL-12 with its receptor, which also activates the JAK-STAT signaling pathway and IFN-α [75]. Due of the significant toxic consequences that cancer patients experienced following systemic IL-12 injection, both in vivo and ex vivo methods that use viral and non-viral vectors to stimulate cytokine production at the TME have been developed. Notwithstanding the difficulties in achieving modest antitumor effects through gene-induced expression mediated by nanoparticles, the observed severe toxicity associated with elevated serum levels of IL-12 caused a reorientation toward anticancer therapies that combine the effects of IL-12 with other antitumor strategies, such as the synergistic effect of IL-12 with other cytokines, like TNF-α, or GM-CSF, using anti-angiogenic factors, like VEGF inhibitors, suicide gene therapy, or chemotherapy [75,76].

Targeting Angiogenesis

Angiogenesis signals, such as vascular endothelial growth factor (VEGF), fibroblast growth factor-2 (FGF-2), angiopoietins, or IL-8, are secreted in response to the hypoxia experienced in the tumor due to the unchecked proliferation of tumor cells. This ensures the availability of oxygen and nutrients [77-79]. To combat tumor angiogenesis, two main approaches are being used: downregulating the expression of pro-angiogenic proteins like VEGF and upregulating the expression of anti-angiogenic factors such TSP-1s, endostatin, or angiostatin. The intricacy of the angiogenic system limits the potential application of angiogenesis targeting for cancer treatment, which is mostly focused on the injection of tailored antibodies that disrupt angiogenic signals. In fact, blocking a single angiogenic critical player may trigger additional angiogenesis routes or even

different vascular channels that resemble endothelium [79].

Targeting for Fibroblasts

Cancer is viewed as a "wound that never heals" due to inflammation at the TME, which causes fibroblasts to differentiate into myofibroblasts, also known as CAFs in the context of tumors [80]. CAFs are a diverse population that arises from several stimuli at the TME, such as oxidative stress, local hypoxia, and growth factors released by immune system and tumor cells. When it comes to the advancement of tumors, CAFs promote tumor cell proliferation, immunosuppressive TME induction, and enhanced ECM desmoplasia [80,81]. In recent years, a number of anti-CAF immunotherapeutic strategies for cancer treatment have been put forth. These strategies include targeting the CAF-derived extracellular matrix (ECM) proteins and related signaling pathways, as well as removing or silencing the fibroblast activator protein+ (FAP+) [82]. In addition to being expressed in CAFs in the majority of solid tumors, FAP is a type 2 dipeptidyl peptidase that plays critical functions in hematopoiesis and the preservation of normal muscle mass [83]. Hence, although FAP targeting CAR-T cell therapy led to tumor regression because of increased anti-tumor immunity, it may also result in immunosurveillance failure and changes in normal tissues, which could lead to cachexia and deadly toxicity anemia [84-86].

Targeting Tumor Cells Derived Exosomes

Exosomes are nanovesicles that play significant roles in intercellular communication and are produced by cells using the endosomal pathway. They consist of an exosomal lumen made up of proteins and nucleic acids, such as mRNA and miRNAs, and their content varies depending on the origin cell's physiological state [84]. They are constructed of a lipid membrane. Crucially, exosomes induce phenotypic changes contingent on the exosomal cargo after being internalized by a secondary cell [85,86]. Exosomes generated from tumor cells often secrete more of them than normal cells do, and they facilitate the growth of tumors by causing angiogenesis, CAF transformation, tumor escape to the immune system, and malignant transformation in normal cells. Therefore, attempts are being made to prevent the release and uptake of exosomes produced by tumor cells [87]. It's interesting to note that suppressing Rab27, a protein involved in the transfer of the late endosome from the nucleus to the plasmatic membrane, in melanoma cells led to an accumulation of miR-494, which in turn suppressed the malignant phenotype by inducing apoptosis. Exosomes can also impede the spread of malignancy by acting as antigens in tumor vaccinations. A fascinating work by Squadrito et al. described an extracellular vesicle internalizing vector (EVIR) based on lentivirus that encouraged DCs to selectively take up extracellular vesicles and effectively display the tumor antigens to T cells [88].

Table 1: Approved gene therapy products

Year of Approval	Trade name	Manufacturer	Vector	Transferred gene	Indication	Approving Agency	References
2022	Carvykti (ciltacabtagene autoleucel)	Legend Biotech	lentivirus	BCMA CAR	Relapsed or refractory multiple myeloma	FDA	[89]
2021	(elivaldogene Skysona autotemcel / Lenti-D)	bluebird bio	Lentivirus	ABCD1 gene	uvenile Cerebral Adrenoleukodystrophy	EMA	[90]
2021	Carteyva (Relma-cel/ relmacabtagene autoleucel)	JW Therapeutics	Lentivirus	CD19 CAR	Relapsed or refractory diffuse large B cell lymphoma	SFDA	[91]
2021	Delytact (teserpaturev) (G47Δ)	Daiichi Sankyo	HSV-1	Triple-mutated, replication conditional oncolytic virus	Malignant Glioma	Japan	[92]
2021	ARI-0001	Hospital Clinic	Lentivirus	CD19 CAR	Adult relapsed/ refractory acute lymphoblastic leukemia Ex-vivo (T cell)	Spain	[93]
2021	Abecma (Idecabtagene vicleuel)	bluebird bio	Lentivirus	BCMA CAR	Multiple myeloma	FDA, Canada, EMA, UK, Japan	[94]
2021	Breyanzi (lisocabtagene maraleuce)	Celgene (Bristol Myers Squibb)	Retrovirus	CD19 CAR	Relapsed or refractory diffuse large B cell lymphoma; follicular lymphoma	FDA, Japan	[95]
2020	Leqvio (inclisiran/ ALN-PCSsc,	Alnylam	RNA	Anti-sense oligonucleotide (siRNA) against	Primary hypercholesterolemia	EMA, UK, Australia, Canada, Israel, FDA	[96]

	ALN60212)			proprotein convertase subtilisin Kexin type 9 (PCSK9)			
2020	Libmeldy (Atidarsagene autotemcel)	Orchard Therapeutics	Lentivirus	ARSA (arylsulfatase A) gene	Metachromatic Leukodystrophy	EMA, UK	[97]
2020	Tecartus (brexucabtagene autoleucel/ KTE-X19)	Kite Pharma (Gilead)	Retrovirus	CD19 CAR	Relapsed/refractory mantle cell lymphoma	FDA, EMA, UK	[98]

CONCLUSIONS:

One interesting and promising method of treating several diseases, including cancer, is done by gene therapy. At the moment, the majority of gene therapy methods are restricted to ex vivo gene transfer**10.5281/zenodo.11319242** techniques or the local delivery of the gene transfer vector. The low transduction effectiveness and minimal vector distribution throughout the tissue continue to be one of the hurdles in gene therapy. It should be stressed, nonetheless, that attention must also be paid to the process of producing these vectors, in addition to vector development itself. The production of viral vectors is expensive since it requires laborious downstream purification processes, which has shown to be difficult. Furthermore, the idea of employing gene therapy as a stand-alone treatment has not shown to be as effective as anticipated. Thus, combination therapy which may provide extra benefits in cancer gene therapy should be taken into consideration in conjunction with other novel medicines or currently used conventional methods.

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