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Review

Gene Therapy Approaches in Hematological Malignancies: Current Strategies and Future Directions

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Abstract

Hematological malignancies, such as leukemia, lymphoma, and myeloma, are cancers originating in the bone marrow and lymphatic system, marked by the uncontrolled growth of blood cells. Gene therapy offers a revolutionary treatment approach by directly targeting genetic mutations and boosting the body's anti-tumor immune responses. This study aims to provide a comprehensive overview of hematological cancers and explores the current and emerging gene therapy strategies that are being investigated for their treatment. It also provides a detailed overview of gene delivery systems, their principles, types, and recent advancements in gene therapy as a potential treatment strategy. It provides a detailed analysis of gene delivery systems, therapeutic modalities, and clinical applications, with a focus on chimeric antigen receptor t-cell therapy (CAR-T), CRISPR-Cas9, and RNA interference (RNAi) technologies. It highlights recent advances in gene delivery, including viral and non-viral vector systems, along with advanced techniques like gene editing and gene silencing. Special attention is given to cutting-edge techniques such as CRISPR-Cas9, CAR-T cell therapies, and RNA interference. The article concludes by discussing current hurdles and prospects of gene therapy, emphasizing its immense potential to transform the treatment for hematological cancer.

Keywords

Hematological malignancies, Gene therapy, CRISPR-Cas9, Chimeric antigen receptor T-cell therapies, Gene delivery

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1. Introduction

Hematological malignancies account for around 7% of global cancer incidence; they are also the fourth greatest cause of cancer mortality [1]. Hematological malignancies refer to a group of cancers that affect the manufacture of blood cells. These types of cancers normally start in the bone marrow, where blood is produced, and are associated with fast-growing, abnormal blood cells. According to GLOBOCAN 2023, hematological cancers account for nearly 1.3 million new cases and over 700,000 deaths globally each year. The incidence is rising, particularly in low- and middle-income countries due to increased environmental exposures and limited early diagnosis. Leukemia arises from either the myeloid cell line or the lymphoid cell line that normally produces B lymphocytes (B cells), T lymphocytes (T cells), Natural killer (NK) cells, and plasma cells. These cancers result from mutations of DNA in blood cells and cause irregular cell division that interferes with the blood's capacity to fight infections or support oxygen transportation. Leukemia arises from either the myeloid cell line that normally gives rise to granulocytes, erythrocytes, thrombocytes, macrophages and mast cells or the lymphoid cell line that normally produces B cells, T cells, NK cells, and plasma cells [2]. Hematological malignancies were first categorically formally acknowledged in the early part of the nineteenth century. The first milestone was when Thomas Hodgkin described Hodgkin's lymphoma in 1832, which started a new classification in blood cancer [3]. It was only by the end of the 19th century that various forms of leukemia were distinguished, considering that the various diseases constitute different conditions.

Hematological Cancer is a collective term used to qualify several different types of cancers. This group consists of cancers of the bone marrow, blood cancer, and cancer of the lymphatic system and all the details are described in Table 1. Leukemia begins in the bone marrow and is the most commonly occurring hematological cancer, along with myeloma which also starts in the bone marrow as well as lymphoma, beginning in the lymphatic system. Since leukemia and myeloma develop in the bone marrow, these tumors can impair the marrow's capability to manufacture healthy blood cells, such as white blood cells, red blood cells, and platelets. This can result in recurrent infections, anemia and bleeding tendencies. Lymphomas, which may manifest as enlargement of lymph nodes, can also compromise the body's immune response to infections. Further, myelomas also produce a factor that leads to the deterioration of bones, while the excess deposition of proteins can cause other symptoms in other body parts [4].

Table 1. Types of hematological malignancies.

Types of hematological malignancies	Definition	Symptoms	Diagnosis	Treatment	Ref.
Leukemia	A blood cancer affecting bone marrow, causing the production of abnormal white blood cells (blasts). Classified into four main types: acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), and chronic myeloid leukemia (CML).	Fever, fatigue, weight loss, flu-like symptoms, joint or back pain, anemia, petechiae, and lymph node enlargement.	Blood tests (CBC), bone marrow biopsy, lymph node biopsy for staging, imaging (X-ray, magnetic resonance imaging (MRI), ultrasound, computed tomography (CT)), genetic testing (e.g., SPRED1 gene).	Chemotherapy (induction, consolidation, maintenance), radiation therapy, intra-arterial chemotherapy for central nervous system (CNS) involvement, stem cell transplantation for severe cases.	[4]
Lymphoma	Cancer of lymphocytes, forming tumors in lymph nodes, bone marrow, spleen, and other organs. Includes Hodgkin lymphoma (Reed-Sternberg cells) and non-Hodgkin lymphoma (T- or B-cell origin.	Weight loss, fever, night sweats, swollen lymph nodes, extranodal symptoms (e.g., liver, bone, CNS), fatigue, itching, loss of appetite.	Physical exam for swollen lymph nodes, lymph node biopsy, immunophenotyping, cytogenetic studies, bone marrow biopsy, imaging (CT, positron emission tomography (PET), Gallium scans for staging).	Chemotherapy (e.g., ABVD, MOPP for Hodgkin; CHOP for non-Hodgkin), radiation therapy, bone marrow transplantation, and stem cell transplantation. Supportive therapies (e.g., acupressure, fucoidan for relief).	[5]
Myeloma	Cancer of plasma cells in bone marrow, leading to overproduction of abnormal plasma cells and bone tumors. Often associated with exposure to toxic substances or radiation, though cause is unclear.	Anemia, pale skin, fatigue, shortness of breath, bone pain, fractures, frequent infections.	Blood tests, bone marrow biopsy, imaging (X-rays, MRI for osteolytic lesions), immunological tests for M-proteins in serum/urine, detection of Bence Jones proteins in urine.	Bisphosphonates (e.g., clodronate, pamidronate, zoledronic acid) to prevent bone weakening, pain relief, autologous/allogeneic bone marrow or stem cell transplantation in advanced cases.	[6]

In this review, we will provide an overview of gene therapy approaches and applications in the treatment of hematological malignancies and explain the fundamental principles and mechanisms of gene therapy. We will also

describe the different strategies employed in gene therapy for cancer treatments and a complete overview of these therapeutic strategies targeting tumor is illustrated in the Figure 1.

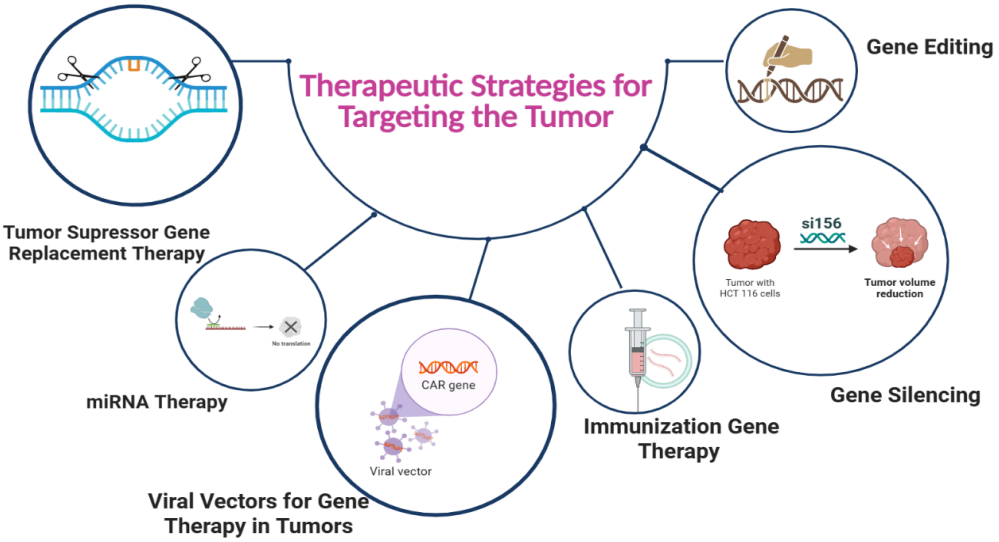

Figure 1. Therapeutic strategies targeting the tumor.

2. Gene Therapy

Gene therapy is a method of treatment that involves adding DNA to a person's body to fix or replace a defective gene that is responsible for causing a disease, especially when other treatments, like medications, are not working for that disease [7]. Gene therapy can be done either *in vivo* (directly delivering an altered virus with the gene into the patient's body) or *ex vivo*, genetically modifying stem cells outside the body and then putting them back in [8]. Gene therapy delivery systems consist of three parts: a plasmid that controls how the gene works within the cell, the gene itself (which produces the necessary protein), and a delivery system (such as the modified virus) that helps bring the gene into the body. For gene therapy to work, the new gene needs to stay stable within the host's cells [9]. The American Medical Association (AMA) notes that there are around 4,000 diseases linked to genetic issues. Some of these include cancer, AIDS, cystic fibrosis, Parkinson's and Alzheimer's diseases, amyotrophic lateral sclerosis, heart disease, and arthritis [10].

Three types of gene therapy are somatic, germline, and preventive or vaccination gene therapy There are different mechanism of actions accompanied by each type of gene therapy as described in Table 2.

2.1 Somatic Gene Therapy

Transferring a gene to a bodily cell that does not aid in reproduction is known as somatic gene therapy. It takes place in identified body cells. The altered genes do not get passed to the other generations.

2.2 Germline Gene Therapy

The germline method involves applying a DNA fragment to bodily parts that allow the human body to produce sperm or eggs. It occurs in all cells of the body. It eliminates genetic disorders from an entire population.

2.3 Preventative or Vaccination Gene Therapy

Vaccination gene therapy is the process of fixing mutated genes linked to a certain illness before the disease manifests itself. It eliminates the likelihood of developing diseases.

Somatic gene therapy can be divided into *in vivo* and *ex vivo* techniques [11]. *Ex vivo* (cells get altered outside the body and then get injected back into the body) and *in vivo* (It is the process of replacement of faulty genes that takes place within the body cells) [12]. Gene therapy utilizes many strategies, i.e, augmentation, inhibition, and cell destruction. Augmentation and inhibition are examples of *in vitro* gene manipulation approaches since they do not require the deficiency to be removed [13].

Inhibition strategy is useful for illnesses with unsuitable gene activities, such as cancer, infections, and genetically transmitted diseases. The method undermines the inappropriate DNA's impact on the body cells [14]. Destruction of abnormal cells is a suitable technique for cancer patients since it eradicates the spread of illness within the human body.

Table 2. Gene therapy approaches for cancer treatment.

Gene therapy approach	Mechanism	Applications	Advantages	Challenges	Ref.
Immunomodulation	Modifies immune cells (e.g., T cells) to recognize and attack cancer cells more effectively.	Used in chimeric antigen receptor T (CAR-T) cell therapy and T cell receptor (TCR)-engineered T cells for leukemia and lymphoma	Enhances the body's immune response; targeted approach with potential for long-lasting effects.	Risk of severe side effects (e.g., cytokine release syndrome); requires personalized treatment.	[15]
Suicide Gene Therapy	Introduces a gene that makes cancer cells susceptible to specific drugs, allowing for targeted killing.	Utilizes genes like HSV-tk to enable the selective destruction of modified T cells if needed	Provides a safety mechanism to eliminate modified cells if adverse effects occur.	Requires careful monitoring; effectiveness depends on the delivery method and timing.	[16]
Oncolytic virotherapy	Uses genetically modified viruses that selectively infect and kill cancer cells while stimulating an immune response.	Emerging applications in various hematological malignancies	Dual action of direct tumor cell lysis and immune activation against cancer	Limited by potential immune responses against the virus; requires robust viral delivery systems.	[17]
Gene transfer for cytokine production	Introduces genes encoding cytokines to enhance anti-tumor immunity or modify tumor microenvironments	granulocyte-macrophage colony-stimulating factor (GM-CSF) expressing vaccines have shown promise in clinical trials for CML and other leukemias	Can improve immune system engagement with tumors, potentially leading to better outcomes.	Delivery methods can be complex; may not work for all patients or tumor types	[18]
Targeted Gene Editing	Techniques like CRISPR/Cas9 are used to correct genetic mutations in cancer cells or modify immune cell receptors.	Potential applications in genetically modifying hematopoietic stem cells or T cells	High specificity in targeting genetic alterations; potential for permanent corrections in some cases.	Ethical concerns and technical challenges in editing human genomes; risk of off-target effects.	[19]

3. Gene Addition

Gene addition is one of the basic gene therapies whereby a healthy gene is incorporated into a patient's cells to complement a non-functional gene. It has been well utilized in genetic disorders and numerous kinds of cancer, such as hematological malignancies, including leukemia, lymphoma, and multiple myeloma. The aim is to reprogram the faulty gene or to improve the body's ability to fight cancer by providing the cells with a new genetic code. Gene therapies also use vectors that can successfully transport genes for treating diseases, which are viral and non-viral, and the third is a hybrid of both. Viral delivery employs viruses to deliver therapeutic genes into human cells. Viral vectors are adenoviruses, retroviruses, adenovirus-associated viruses (AAVs), bacteriophages, and lentiviruses (LVs). While non-viral vectors, including gene guns and microinjection, use physical or chemical means, such as liposomes and polymers, to introduce DNA, resulting in less death compared with viral vectors. Therefore, viral vectors, despite drawbacks like high immunogenicity, safety concerns, and production challenges, while their unparalleled transfection efficiency is one of the most important advantages for gene delivery. In contrast, non-viral vectors are gaining popularity due to their larger gene-carrying capacity, reduced immunogenicity, enhanced safety profile, and suitability for mass production [20].

3.1 Viral Delivery Method

Recently, viral vectors of gene therapy have been mostly used *in vitro* and *in vivo* due to their high transfection efficiency and stable transgene expression. Commonly used viral vectors include LVs, AAVs, adenoviral vectors (AdVs), and bacteriophages.

3.1.1 Lentiviral Vectors

LVs are particularly important for gene addition therapy, especially for hematological malignancy, because of their ability to integrate their therapeutic gene into the genome of the recipient host and thereby support long-term gene expression. It is especially useful for the expression of conditions that require constant expression of genes, such as the hematopoietic stem as well as the immune cells. LVs can infect both cycling and quiescent cells, which may be advantageous in the treatment of leukemia/ lymphomas and more generally [21]. The complete process of CAR-T cell therapy is described in detail in Figure 2. Their incorporation concerning CAR-T cell therapies has been radical, for example, Genetically Modified T-cells available for cancer detection, such as Kymriah or Yescarta – Leukemia and

Lymphoma treatment to be specific. Tisagenlecleucel targeting CD19 protein on B-cells changes the course of children with relapsed or refractory ALL and stops therapy with pediatric ALL [21-22]. Further refining of LVs is still ongoing in attempts to optimise the CAR-T cell production as well as its anti-tumor effects. Lentiviral vectors have also been applied to Gene therapy of Fanconi Anemia, which is a genetic disorder with a high incidence of leukemias, and where a functional gene is indispensable [23].

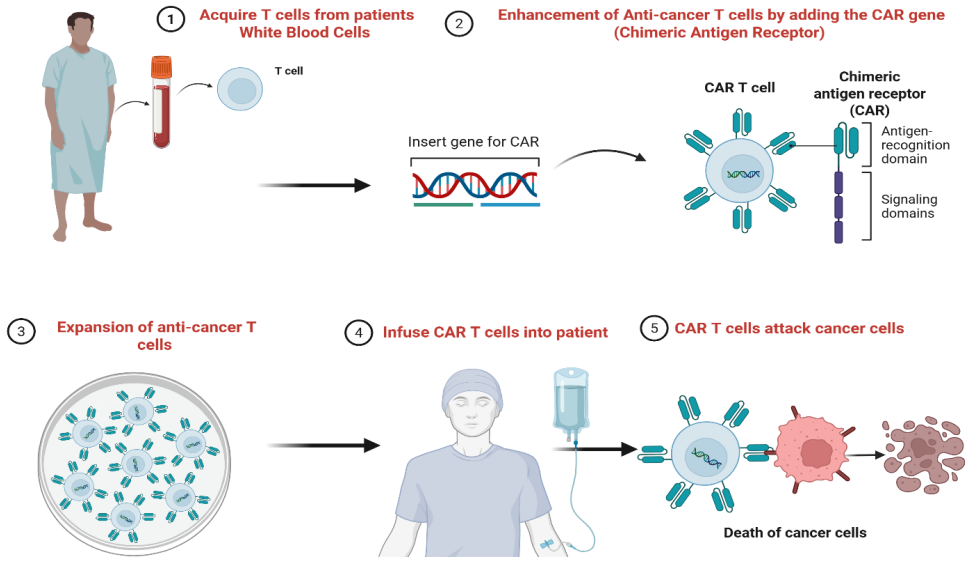

Figure 2. CAR-T cell therapy process.

3.1.2 Adenovirus-associated Virus Vectors

AAVs are non-integrating, double stranded DNA virus highly valued in gene therapy due to its favorable biological characteristics and efficient gene transfer viral vectors and well suited for maintaining long-term transgene expression, not integrating within the target cell genome; thus, AAVs are useful in virtually all hematologic diseases where the vector doesn't have to integrate into the host genome [24].

3.1.3 Adenoviral Vectors

AdVs are unenveloped double-stranded DNA virus. Adenoviral vectors are widely used in gene delivery due to its stability, mass loading capacity, and efficiency. They are also used to transduce larger genes, but cannot integrate into the host DNA and are tagged with a strong immune response, which limits the long-term treatment by any of this vector type [25].

3.2 Non-viral Delivery Method

Higher interest is also being shown towards applied nonviral gene-adding techniques that would help replace the conventional viral approaches in the treatment of hematological cancers. These approaches use many different non-viral vectors as well as methods to escalate or alter the immunomodulatory characteristics of the gene-transferred T-cells and other immune cells, particularly in the setting of CAR-T cell treatments.

3.2.1 Electroporation

Electroporation is a physical method that involves the use of electric pulses to increase the permeability of cell membranes and allow the uptake of nucleic acids. This technique has been found to increase the effectiveness of the non-viral gene transfer the result has been creation of memory T cells that is very vital for long-term immune response against tumors. T cells from ALL or non-hodgkin lymphoma (NHL) patients are extracted from the body and genetically modified by the process of electroporation to produce CAR receptor that identify the CD19 on cancers [26].

3.2.2 Nanoparticle System

Systems of nanoparticulate structures, such as lipid and polymer-based carriers, are being employed to increase nucleic acid delivery efficiency, including mRNA and siRNA. These systems can improve the uptake of cellular and offer a controlled release of therapeutic agents [26]. For instance, functionalized folate nanoparticles exhibit a positive uptake in cancer cells with high expression of folate receptors and increase gene-carrier effectiveness [27].

3.2.3 Lipid Nanoparticle

Lipid nanoparticles have been receiving so much attention because of their capability to encapsulate mRNA and then transfer it into cells. This method is widely applicable in the production of vaccines and appears to apply to cancer through the stimulation of excised animal cells to produce high amounts of proteins without the need for integration into the genome [27].

3.2.4 Peptide-Based Delivery in Multiple Myeloma

Another area where this approach has been used is in multiple myeloma; here, peptides are used to transfect plasmid DNA, which contains codes for anti-tumor proteins, into malignant plasma cells. PML participates in cancer cell apoptosis and, therefore, can reduce tumor volume. There are previous studies that have used cell-penetrating peptides to deliver plasmid DNA, which seemed promising, and this non-viral gene delivery method might become a potential treatment for patients who do not respond to such therapies [28].

4. Gene Silencing

Gene silencing involves inhibiting the expression of particular genes, hence inhibiting the formation of proteins related to diseases. Regarding hematological cancers and malignancies, gene silencing implies several therapeutic options, which stem from a number of hematological cancers are caused by genetic mutations or dysregulated gene expression. Application of gene silencing includes RNA interference (RNAi) and antisense oligonucleotides (ASOs), which are the two main techniques in this category.

4.1 RNA Interference

RNA interference or RNA shall be described as the regulation of gene expression through the exposure of small RNA molecules that degrade mRNA before the mRNA can be translated into protein [8]. This mechanism affects many genes but may give most important sense in this connection, where the majority of neoplastic diseases involve genetic changes or the alteration of expression of particular genes, especially in the class of hematologic neoplasms. Thus, there are two primary approaches to intervention in gene function, including RNA interference and ASOs. Myeloma, in which it is utilized to introduce into the malignant plasma cells plasmid DNA that produces anti-cancer proteins. Some of these proteins induce apoptosis, the death of the cancerous cells and therefore lessens tumor load. The first attempts of cell-penetrating peptides mediating plasmid DNA demonstrated the effectiveness of this non-viral method; therefore, it might be relevant for patients with viral therapy resistance [26,28].

4.1.1 Applications in Hematological Cancer

RNAi has been applied for the knockdown of oncogenes involved in distinct forms of hematological cancer. For instance, siRNAs to BCR-ABL, which encodes proteins in CML, demonstrated potency in downregulating BCR-ABL without interfering with normal BCR or ABL variants [29]. According to research done it has been observed that RNAi is capable of repressing AML1/MTG8 fusion proteins which is common in AML hence, promoting cell differentiation coupled with increased sensitivity to growth factors. This approach has useful in casting light on the distinct function of certain oncogenic pathways in sustaining the tumor. RNAi has been explored to combat drug resistance in hematological cancers by silencing genes associated with resistance mechanisms, such as BCR-ABL in CML. This strategy can enhance the efficacy of existing therapies like imatinib [30].

4.2 Antisense Oligonucleotides

ASOs are short synthetic molecules of nucleic acids intended to interact with pre-messenger RNA sequence, making regulatory sense to a particular gene expression. This approach has enthralled the scientific community in the early stage of therapeutic intervention, especially for genetic diseases and other diseases such as hematologic malignancies. ASO function in a number of ways, for example, RNA degradation, steric blocking or splice modulation. ASOs works by depending on RNA degradation, direct blockade, and splicing regulation [31].

4.2.1 Application in Hematological Cancer

By selective targeting oncogenes implicated in tumor development, ASOs can be associated with cancer therapy. For example, ASOs designed for BCL2 have been considered to implement apoptosis in B-cell malignancies like CLL and NHL. ASOs can also be employed as therapeutic agents that control cytokines or other signaling species that regulate cellular signaling pathways that promote tumor viability and growth. It may also improve the impact of existing treatments by changing the context in which malignant cells survive. ASOs' integration with other treatments, including chemotherapy or immunotherapy, may enhance treatments' therapeutic efficacy. ASOs help in jumping over obstacles in treatment by knocking down resistance genes or increasing the sensitivity to drugs [32].

5. Gene Editing Technologies

Genome or gene editing is a way of genetic engineering where genes that an organism has can be cut, replaced or even replaced by a new one. It is a way of changing or rearranging a limited series of letters in the genetic code of an organism by addition, omission, relocation, exchange or by other means. Contrary to the previous methods of genetic manipulation, which introduced genetic material at any location along a chromosome, gene editing makes it possible for the editor to direct the change to a specific area of the chromosome, thus affecting the desired genes only. Technologies used in gene editing are CRISPR-Cas9, Zinc finger nucleases (ZFNs) and Transcription Activator-Like Effector Nucleases (TALENs).

5.1 CRISPR-Cas9

CRISPR-Cas9 is a cutting-edge type of genome manipulation that enables the addition, deletion, or alteration of specific genes in organisms. It consists of two main components: These components consist of the Cas9 enzyme, which can cut DNA and a single guide RNA (sgRNA) that determines the location of Cas9 to cut. This technology allows researchers to insert and manipulate genes within the genome and, as such, is a powerful technique in all genetic analysis and therapy, particularly for hematological cancers. Therefore, new developments have been applied in the CRISPR-Cas9 system for genome-precise editing in CAR-T cell treatments. This method enables the introduction of genes into specific areas without the risks of insertional mutagenesis, which characterizes viral vectors. When used in clinical trials, non-viral, gene-specific CAR-T cells proved to be highly effective and safe, with a remission rate of 87.5% for aggressive B-cell non-Hodgkin lymphoma [32]. The detailed description of applications and role of CRISPR based system for different types of hematological cancers is described in detail in Table 3.

Table 3. Applications and role of CRISPR in hematological cancer.

Type of cancer	Role	Application	Case studies	Ref.
Leukemia	Disrupts oncogenic signaling, potentially leading to remission	Targeting the BCR-ABL fusion gene in CML	A study demonstrated successful targeting of BCR-ABL with CRISPR-Cas9 in CML cell lines, resulting in reduced proliferation and increased apoptosis.	[33]
	Improves the efficacy of CAR-T cell therapies	Editing T-cells to enhance their ability to target and kill leukemia cells	Research showed enhanced anti-leukemic activity of CRISPR-engineered T-cells in mouse models of leukemia.	[34]
Lymphoma	Enhances the persistence and efficacy of CAR-T cell therapy	Modifying CAR-T cells to improve specificity against B-cell lymphomas	A case study reported successful engineering of CAR-T cells using CRISPR-Cas9 to target CD19 in B-cell lymphoma, leading to significant tumor.	[34]
	Overcomes immune checkpoint inhibition	Targeting genes like PD-1 in T-cells to enhance anti-tumor immunity	A study highlighted the knockout of PD-1 in T-cells via CRISPR-Cas9, resulting in improved anti-tumor responses in lymphoma models.	[35]
Myeloma	Reduces tumor growth and survival	Disrupting MYC oncogene expression to inhibit the proliferation of multiple myeloma cells	Research indicated that CRISPR-Cas9 targeting of MYC led to decreased viability of myeloma cells *in vitro*.	[36]
	Improves targeted therapy effectiveness	Engineering immune cells to express CARs targeting specific antigens on myeloma cells (e.g., BCMA)	The study demonstrated the successful use of CRISPR-Cas9 to create BCMA-targeted CAR-T cells, showing promising results in preclinical models of myeloma.	[37]

One of the concerns in developing CRISPR-based therapy is the specificity of CRISPR systems. This issue originates from significant evidence that CRISPR-Cas systems might cause unwanted DNA changes. These undesired modifications can be caused by both on- and off-target activities, resulting in minor insertions or deletions as well as significant structural variants (SVs). As a result, properly testing the genome-wide specificity of CRISPR tools is critical to ensuring their safety in therapeutic applications. Off-target effects remain a critical challenge in the CRISPR-Cas9 gene editing system. However, these can be minimized through in silico prediction tools such as Cas-Offinder and optimized sgRNA design, which enhance target specificity. Engineering high-fidelity Cas9 variants (e.g., eSpCas9, SuprFi-Cas9) has significantly improved precision by reducing unintended DNA cuts. In addition, alternative editing tools like base editors (CBEs and ABEs) and prime editors (PEs) enable precise nucleotide changes without inducing double-strand breaks (DSBs), further lowering off-target risks. Anti-CRISPR proteins also offer a promising layer of control by selectively inhibiting CRISPR activity, enhancing safety [33].

5.2 Transcription Activator-Like Effector Nucleases

TALENs are a complex type of genome editing tools that allow editing some DNA sequences in different organisms. They consist of two main components: TALEs that specifically target DNA sequences to bind and a nuclease which can cleave the DNA, most frequently FokI. This technology helps researchers to make specific changes to genes, making

the impacts relevant for medical, farming, and biological uses. Applications and role of TALENs in hematological cancers is discussed in Table 4.

Table 4. Applications and role of TALENs in hematological cancers.

Types of cancers	Role	Applications	Case studies	Ref.
Leukemia	create patient-specific models of leukemia to study the disease's progression and test new therapies. They can also be utilized to modify T-cells to CARs that target leukemia cells more effectively.	Engineering T-cells to express CARs targeting leukemia cells (e.g., CD19). Targeting genes like FLT3 to understand their role in leukemia progression.	Researchers utilized TALENs to engineer T-cells from patients with ALL. The modified T-cells were designed to express CARs targeting CD19, a common marker on leukemia cells. Initial results showed promising responses in patients who had relapsed after standard therapies	[37]
Lymphoma	Functional analysis of tumorigenesis-related genes. Enhancing CAR-T cell therapies for better targeting.	Disruption of genes involved in lymphoma development to identify therapeutic targets. Modifying immune checkpoints like PD-1 to improve CAR-T cell function against lymphoma cells.	A study demonstrated the use of TALENs to knock out specific oncogenes in lymphoma cell lines, revealing essential pathways involved in cell proliferation and survival. This research provides insights into potential therapeutic targets for treating aggressive lymphomas	[38]
Myeloma	Investigation of genetic alterations and drug resistance mechanisms.	Enhancing sensitivity of myeloma cells to existing therapies.	Researchers applied TALEN technology to disrupt genes associated with drug resistance in multiple myeloma cells, enhancing sensitivity to existing therapies and potentially improving patient outcomes. Knocking out genes like TRAC and CD52 to enhance CAR-T cell efficacy and reduce rejection.	[39]

5.3 Zinc Finger Proteins

Zinc finger proteins (ZnFs) are small protein domains that contain 20 to 100 amino acids and stabilize the molecule through zinc ions tied to cysteine and histidine residues. First discovered in the transcription factor IIIA of Xenopus laevis, ZnFs are known to be promiscuous in that they bind with practically any type of ligand, DNA, RNA, and proteins. Their main role is to regulate particular contacts with DNA sequences which are significant in transcription and multiple cellular phenomena, including development, differentiation and reactions to stimuli [40].Applications and role of ZnFs in different hematological cancers is described in Table 5.

Table 5. Applications and role of ZnFs in hematological cancers.

Type of cancer	Role	Application	Case studies	Ref.
Lymphoma	Regulation of gene expression involved in cell proliferation and survival. Alterations in ZnF Expression can contribute to Leukemogenesis.	Targeting zinc finger nucleases (ZFNs) for gene editing to correct mutations associated with leukemia. Potential use as bioma-rkers for diagnosis and prognosis.	A study demonstrated the use of ZFNs to edit the genome of hematopoietic stem cells from patients with ALL. The research showed promising results in correcting genetic mutations linked to the disease, enhancing the potential for personalized therapies	[41]
	ZnFs involved in immune response modulation and apoptosis regulation. Specific ZnFs may act as oncogenes or tumor suppressors.	Gene therapy approaches using ZFNs to target oncogenic pathways. - Development of ZFN-based therapies to enhance immune response against lymphoma cells.	Research focused on using ZFNs to target specific genes involved in B-cell lymphoma. The study highligh-ted how ZFN technology could be utilized to disrupt oncogenic pathways, offering a novel therapeutic strategy that could improve patient outcomes	
Myeloma	ZnFs implicated in the regulation of plasma cell differentiation and survival. - Certain ZnFs are associated with drug resistance mechanisms.	Use of engineered ZFNs to modify myeloma cells for improved treatment outcomes. - Potential for ZFN-mediated targeting of drug resistance genes.	A recent investigation explored the role of specific ZnFs in multiple myeloma cells' resistance to conventional therapies. The findings suggested that manipulating these ZNFs using targeted gene editing could sensitize myeloma cells to treatment, providing a basis for future therapeutic interventions	[42]

6. FDA Approvals and Clinical Trials

6.1 Kymriah (Tisagenlecleucel)

The first FDA-approved CAR-T cell-based gene product, Kymriah, is used to treat B-cell ALL that has relapsed. This treatment uses lentivirus-modified T cells from the patient to express a chimeric antigen receptor (CAR). Together with intracellular signaling domains 4-1BB (CD137) and CD3 zeta, which are joined by a CD8 transmembrane hinge, this CAR is designed to precisely target CD19 using a murine single-chain antibody fragment (scFv).

Kymriah uses the CD3 domain to start its anti-tumor action when it binds to cells that express CD19. This anti-tumor action is further enhanced by the 4-1BB co-stimulatory domain. Cells with diffuse large B-cell lymphoma (DLBCL) and other B-cell lymphomas have the 95-kD glycoprotein CD19 as a surface antigen. Phase 2 clinical trials for refractory DLBCL with Kymriah demonstrated encouraging outcomes. At three months, a 50% response rate was noted. After six months, 43% of patients had a full response [43].

6.2 Yascarta (Axicabtagene Ciloleucel)

It is another CAR-T cell therapy used to treat aggressive non-Hodgkin lymphoma. *Ex vivo* modified autologous T cells specific to the CD19 antigen are infected with a gamma-retroviral vector. It encodes a CAR with an extracellular murine anti-CD19 single-chain variable fragment linked to a cytoplasmic domain that includes CD28 and CD3-zeta co-stimulatory domains [44].

6.3 Tecartus (Brexucabtagene Autoleucel)

Brexucabtagene autoleucel has been approved by the FDA for the treatment of people with relapsed or refractory mantle cell lymphoma (MCL) or B-cell ALL. It is a modified CAR-T cell immunotherapy. The patient's own T cells are extracted and genetically transformed *ex vivo* to produce a CAR that targets CD19. The anti-CD19 CAR consists of a murine anti-CD19 single-chain variable segment coupled to CD28 and CD3-zeta costimulatory domains. Tecartus attaches to both cancer cells with CD19 and normal B cells. When CAR-T cells are activated, the CD28 and CD3-zeta costimulatory domains initiate a downstream signaling cascade that causes T-cell activation, proliferation, accumulation of effector abilities and secretion of inflammatory cytokines and chemokines. This results in the disintegration of cells that express CD19 [45].

6.4 Breyanzi

Breyanzi is a CAR-T cell treatment that targets CD19, a surface antigen found on both cancerous and normal B cells. Breyanzi's CAR has multiple essential components, including an FMC63-derived single-chain variable fragment for CD19 recognition, an IgG4 hinge region, a CD28 transmembrane domain, a 4-1BB costimulatory domain, and a CD3 zeta activation domain. In addition, the CD3 zeta domain stimulates T-cell activation and antitumor cytotoxicity, but the 4-1BB costimulatory signal promotes T-cell proliferation, persistence, and survival. When CAR T cells connect to CD19, they get activated, multiply, and exude proinflammatory cytokines, eventually destroying cancer cells [46].

6.5 Abecma (Idecabtagene Vicleucel)

Abecma is a CAR-T cell treatment that targets the B-cell maturation antigen (BCMA). Its CAR design includes an anti-BCMA single-chain variable fragment for antigen recognition, a transmembrane domain, a CD3-zeta signaling domain for T-cell activation, and a 4-1BB costimulatory domain to enhance cell survival and function. It has been approved by the FDA to treat adult patients with relapsed or refractory multiple myeloma who have previously had four or more lines of therapy, including an immunomodulatory drug, a proteasome inhibitor, and an anti-CD38 monoclonal antibody [47].

6.6 ZUMA-1

It is a clinical trial in which evaluated the effectiveness of axicabtagene ciloleucel, a CAR-T cell treatment, in treating patients with relapsed or refractory large B-cell lymphoma was assessed in this clinical trial. The result showed an excellent response rate; the FDA approved the treatment. Long-term follow-up studies such as the ZUMA-1 trial report sustained remission rates of over 40% after 5 years in relapsed/refractory large B-cell lymphoma, with real-world studies confirming these clinical outcomes [48].

7. Challenges in Gene Therapy

Gene therapy faces technical challenges in modern medicine. It is difficult to introduce new genes into cells *in vivo* and *in vitro* and keep them working. The following are the main challenges associated with gene therapy.

7.1 Safety Risks

A hypothetical safety concern that the recombination of lentiviral vectors to create replication-competent viruses has not been observed. Therefore, a primary safety concern for hematopoietic stem cell gene therapy remains the genotoxicity associated with integrating vectors.This was tragically illustrated in early trials where gamma-retroviral vectors led to leukemia in some patients, while lentiviral vectors have demonstrated a significantly improved safety record in many clinical trials. It is vital to recognize that site-specific gene editing has several genotoxicity hazards, including as accidental insertions, deletions, and off-target effects, even if it is suggested as a way to lessen genotoxicity in comparison to randomly integrating lentiviral vectors. However, the practical use of any gene editing strategy requires an accurate assessment of these particular dangers [49].

7.2 High Cost

Hematopoietic gene therapy is cost-effective. Viral vectors are mostly used in gene therapy to deliver genes. These can trigger immune responses and can cause the destruction of the vector and causing inflammation. The clinical expenditures are fairly normal and include patient screening, blood tests, central line insertion, conditioning chemotherapy, and post-transplant care. The unique costs derive from the manufacturing of the cell product, which includes the gene therapy vector, cell processing (CD34 selection, cell culture, and testing), GMP facility use, and regulatory compliance. Commercial production costs are much greater than academic settings due to stricter documentation requirements, building charges, maintenance, and higher staffing levels [50].

7.3 Immune Response

Our bodies are excellent at defending against infections. However, gene therapy employs unique carriers (vectors) that must evade this defense system. If they do not, the body's reaction may cause severe illness or death. Researchers use several strategies to prevent immune reactions, including delivering viruses to cells outside the patient's body, temporarily suppressing the patient's immune system with drugs during treatment, using the lowest effective viral dose, and prioritizing vectors that are less likely to elicit an immune response [51].

7.4 Ethical Concern

Researchers and Bioethicists warned that genome editing is a new and unpredictable technology with little understanding of gene regulation and embryonic development, making the effects of germline therapy potentially lethal. Even though CRISPR/Cas systems have proven to be effective for somatic cell applications, their usage in human reproductive gene editing for clinical purposes is still poorly known, therefore, long-term implications cannot be overlooked. Gene editing in human embryos poses a significant danger of developing permanent diseases and disabilities in both the patient and their progeny. In addition, Cas9 targeting is highly selective, yet off-target cleavage can still occur. Furthermore, integrated viral vectors (retrovirus, lentivirus, and adeno-associated viruses) might insert genetic material into unexpected host genome areas, potentially resulting in insertional mutagenesis [52].

8. Future Perspectives of Gene Therapy

Hematopoietic gene therapy has shown promising results in both completed and ongoing clinical trials. This therapy demonstrated its effectiveness in correcting metabolic issues and providing clinical benefits. It led to the regulatory approval. Hematopoietic gene therapy's future is marked by growing accessibility, safety, and precision. Advances in gene editing tools, a better knowledge of hematopoietic stem cell biology, and the shift to *in vivo* techniques have the potential to transform the treatment of a variety of blood and genetic illnesses, providing previously unthinkable therapeutic alternatives. In addition, site-specific *in vivo* genome editing involves directly modifying defective genes within the cell. It shows great promise in current pre-clinical studies and trials. However, this groundbreaking technology is expected to significantly expand treatment possibilities for inborn errors of metabolism in the future [53].

9. Conclusion

One of the cutting-edge therapies for hematological malignancies is gene therapy. The various approaches, which include gene insertion, silencing and editing, provide effective means of addressing the cellular and genetic processes that underlie tumors. Even though there has been a lot of improvement, future research and technical developments could improve these methods even more, resulting in safer, more individualized, and successful treatments. The integration of gene therapies with conventional and emerging cancer treatments, coupled with a strong focus on addressing challenges and ethical considerations, holds the key to transforming the landscape of hematological cancer care and improving the lives of patients.

Conflict of Interest

The authors declare no conflict of interest.

Generative AI Statement

The authors declare that no Gen AI was used in the creation of this manuscript.

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