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Research Article

An Overview of Emerging Trends in Gene Therapy for Cancer Treatment

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Abstract

Clinical trials have long recognized cancer treatment as a top priority. Different approaches have been devised for dealing with tumors of different types and at different stages. When it came to curing cancer, gene therapy was vital. The advancement of genome engineering technologies over the past thirty years has pushed forward gene therapy for the treatment and management of chronic diseases. It is the hope of researchers that one day they will be able to treat individuals with single gene disorders and complicated acquired diseases in a way that is both safe and successful. Gene delivery is a promising new method for detecting, diagnosing, and maybe treating cancer, made possible by recent developments in genetic engineering. Naked nucleic acid-based treatment, targeting microRNAs, oncolytic viral therapy, suicide gene-based therapy, targeting telomerase, cell-mediated gene therapeutics, and CRISPR/Cas9-based therapies are just few of the cancer medicines that have been created and tested in vitro and in vivo. This article provides a critical overview of the present and diverse cancer gene therapy methodologies, as well as a summary of the available viral and non-viral gene delivery mechanisms for gene therapy. In the future, biosafe carriers for gene products will play a crucial role in the prevention of cancer.

Keywords

Gene Therapy, Cancer Treatment, Gene Editing, Tissues

1. Introduction

The recent years, cancer has become a significant public health concern, being the second leading cause of mortality after heart disease [1, 2]. Cancer is characterized by uncontrolled cellular proliferation, resulting in the formation of neoplastic masses [3]. The causes of this phenomenon encompass somatic mutations occurring in cellular signaling pathways located upstream, as well as any mutated gene that expresses cyclin. Despite advancements in conventional cancer treatment, a significant number of individuals continue to suffer to the ailment annually. Malignant tumors pose significant challenges for traditional treatment because of their tendencies for metastasis, recurrence, heterogeneity, and resistance to chemotherapy and radiotherapy [4, 5]. The inherent ability of cancer cells to evade the host's immune system represents an additional factor contributing to the occasional ineffectiveness of treatment interventions. The adverse effects of most conventional cancer treatments have been extensively documented and widely disseminated.

While considering cancer treatment, chemotherapy emerges as the predominant choice. Conventional chemo-

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therapeutic agents have certain limitations regarding their non-specific distribution, resulting in reduced bioavailability, fast elimination from bloodstream, and limited solubility in physiological fluids [6, 7]. Until yet, no cancer therapy has achieved the desired objective of selectively eradicating tumor cells while minimizing damage to adjacent healthy cells and tissues.

According to Hu et al. [8] globally, the number of people diagnosed with cancer is expected to rise as the population increases. Surgical excision followed by chemo-radiotherapy is a standard cancer treatment that has been shown to boost survival rates, but long-term chemotherapy causes more side effects Individual genes or pathways thought to have a role in carcinogenesis can be attacked with gene therapy. Rosenberg et al [9] discussed the evolution of gene therapy as a potential cancer treatment. In the 1990s, the first clinical study of gene therapy was performed to treat cancer. Wang et al., [10] investigated the efficacy of gene therapy as a form of immunotherapy for combating cancer. Oncolytic virotherapy was subsequently developed; this method use viruses to selectively target and kill cancer cells. Recent developments in gene editing tools like CRISPR/Cas9 have paved the way for novel applications of gene therapy in the treatment of cancer Fundamentally, cancer can be attributed by dysfunction of one or more genes. Owing to recent developments in cell and gene therapy, researchers are now able to treat a wider range of conditions, from congenital ones to solid cancers. In the decades since the first gene therapy was produced in 1990s, several products have been licenced thus revolutionizing a new era of gene therapy [11]. Gene therapy significantly point out the root cause of cancer by upregulating or downregulating target genes, thus presenting a wide range of potential therapeutic strategies for this disease. The most substantial challenge to effective gene therapy is the presence of nuclease in the blood and the recognition of foreign nucleic acids, DNA, and RNA detected by the immune system frequently have a short half-life in circulation.

The concept of gene therapy came under considerations after William Johnson coined the term 'gene'. After half century, Francis Crick and James Watson discovered the double helix structure of DNA. In the 1930s, the term "genetic engineering" first arose [12]. Eukaryotic transfection technology has advanced greatly since its commencement in the 1960s, when the basic idea of bacterial gene transfer was developed [13]. Early studies of restriction enzymes and ligases in the 1970s paved the way for modern gene editing [14, 15]. Scientists can use recombinant DNA technology to adapt certain therapeutic genes into engineering vectors. Now that we know viruses can carry genes from one host to another, viral vectors offer a safe and efficient method of gene transfer [16]. Because of these advancements in technology, scientists are now able to construct gene therapy vectors that can deliver precise genetic materials to the mammalian cells of interest.

Clinical trials pertaining to cancer were the most common type of study from 2010 to 2020. Because of their favorable characteristics, including easy accessibility and broad surface contacts, hematological cancers have attracted the most attention from researchers. Cancers of the gastric tract and nervous system account for a significant percentage of patients in gene therapy studies. The most prevalent types of cancer treated with gene therapy include leukemia, lymphoma, melanoma, and multiple myeloma. One of the most well-known and productive applications of gene therapy in immunotherapy is CAR-T cells [17, 18]. T cell transformation leading to surface expression of chimeric antigen receptors (CAR-T cells). The "warheads" of these hypotheses are the chemically resistant single-stranded variable fragments (scFv) of homologous antibodies, which target tumor-related antigens in particular [19]. T cells are fully activated in response to interaction with target antigens because CAR-T cells are endowed with intracellular co-stimulatory domains [20]. This occurs because CAR-T cells are promoted to successive generations. CAR-T cells are among the most promising anticancer tools because of their capacity to activate and expand T cells as well as their scFv selectivity [21]. T cells with altered TCRs function in a similar fashion, with the exception that they also need to activate other cellular elements, such as HLA to become completely active [22]. Promising outcomes have been seen in clinical trials of Phase-3 for the treatment of lymphoma and melanoma using DC vaccines, which employ specialized white blood cells carrying antigens to transfer antigens into host cells [23].

After Wilhelm Johannsen coined the term "gene" [24], the door to gene therapy opened. About fifty years later, Francis Crick and James Watson discovered the double helix structure of DNA. "Genetic engineering" as a field of study dates back to the 1930s [25]. In the 1960s, researchers considered the fundamental basis of bacterial gene transfer and used it to develop eukaryotic transfection technology [26]. The foundation of genetic engineering is the work of restriction enzymes and ligases, which were initially identified in the 1970s [27]. By using recombinant DNA technology, scientists can introduce targeted therapeutic genes into designed vectors [28]. Researchers have found that viral vectors can successfully transport genes from one host to another. Scientists now have the tools to create gene therapy vectors that can deliver therapeutic genes to specific mammalian cells. Various Research Conducted on Gene Therapy is Illustrated in Figure 1.

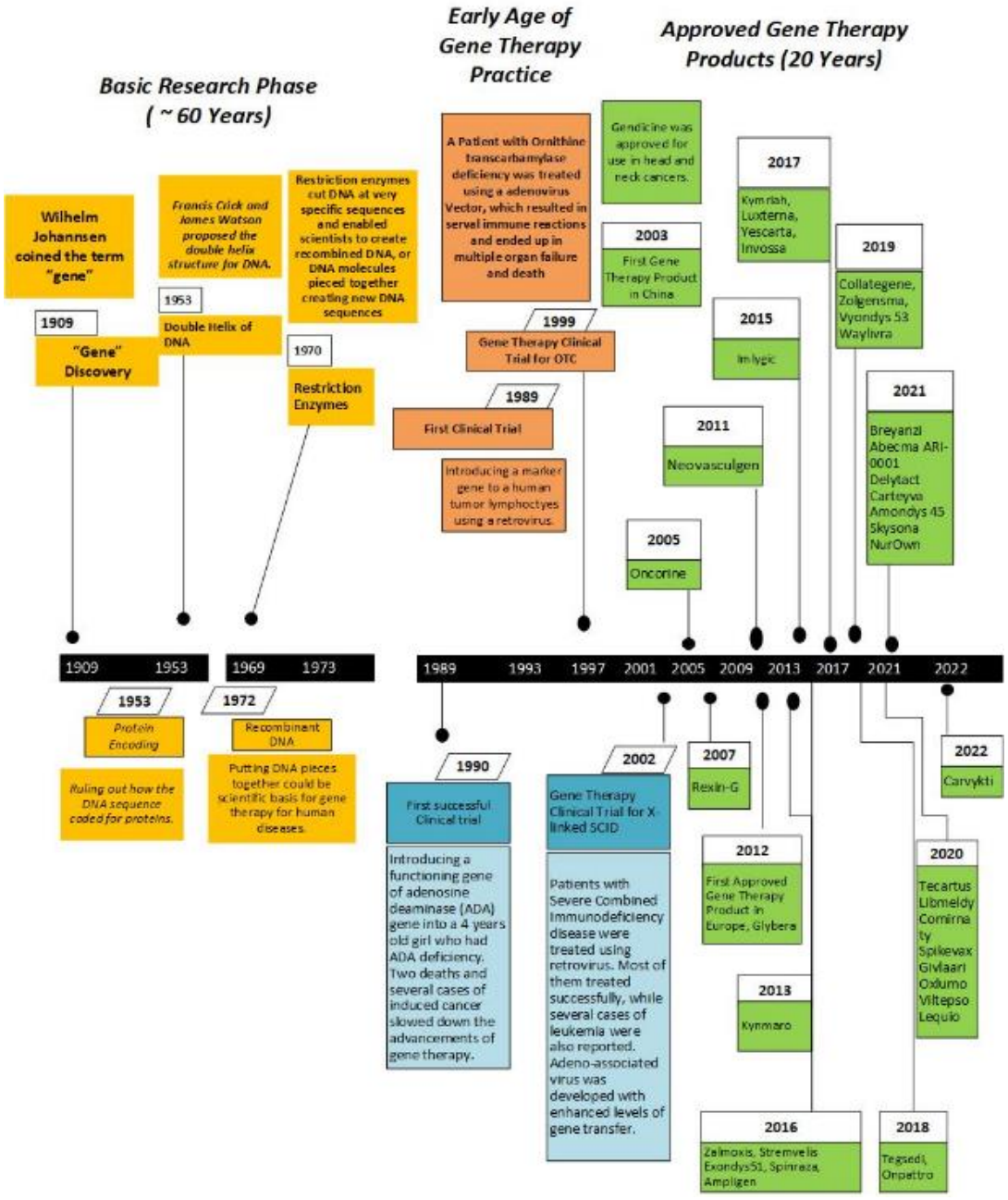

Figure 1. *Research Conducted on Gene Therapy from 1909~2022.*

2. Gene Therapy Strategies for Cancer Treatment

Following are strategies adopted for of Gene Therapy for cancer Treatment:

2.1. Immunotherapy

Cancer treatment has been radically altered by the synergistic convergence of immunotherapy and gene therapy, two pillars of present-day oncology. Antibodies against immunological checkpoints (CTLA-4 and PD-1/PD-L1) have shown impressive efficacy in a variety of cancers by reviving the host immune response against tumor cells [29]. Genetically altered immune cells, such as chimeric antigen receptor (CAR) T cells, have been developed by the combination of gene therapy and immune system modulation to improve tumor identification and cytotoxicity. CD19-targeted CAR-T cells, an example of this approach, have been approved for the treatment of refractory B-cell malignancies [30] Patient-derived T cells are genetically modified to express Chimeric Antigen Receptors (CARs) targeting tumor antigens in CAR-T cell therapy. CARs activate and kill tumor cells by attacking on their targets. CD19-targeted CAR-T therapy is an example of a treatment for hematological malignancies that has shown remarkable effectiveness, resulting in FDA approval and long-lasting reductions. Multiple antigen

recognition domains and fine-tuning of CAR-T cell persistence are two emerging topics in CAR design [31].

2.2. Virotherapy for Cancer

To selectively infect and lyse cancer cells, oncolytic viruses use either naturally occurring or genetically modified viruses. The proliferation of viruses not only destroys tumor cells, but also boosts the immune system's ability to fight cancer. The therapeutic promise of this approach is shown by the FDA-approved oncolytic herpesvirus talimogene laherparepvec (T-VEC) for the treatment of melanoma. There is hope for expanded therapeutic applications thanks to developments in viral engineering that allow for tumor tropism and payload delivery [32]. T-VEC is a revolutionary new way to use virotherapy in the fight against cancer. To induce anti-tumor immune responses while sparing normal tissues, T-VEC is an oncolytic herpes simplex virus type 1 (HSV-1) designed for selective replication within tumor cells. This case study exemplifies T-VEC's promising clinical outcomes and its potential to further the field of virotherapy as an effective cancer treatment option.

2.3. Gene Editing Technologies

CRISPR-Cas9 and other gene-editing technologies provide very specific and adaptable options for treating cancer. Correcting, disrupting, or modulating genetic abnormalities involved in oncogenesis can block tumorigenic signaling pathways. New vulnerabilities in cancer can be found quickly using CRISPR-based screening, which improves target discovery for therapeutic interventions. Off-target effects and delivery optimization are two areas that need extensive study as clinical translation advances [33].

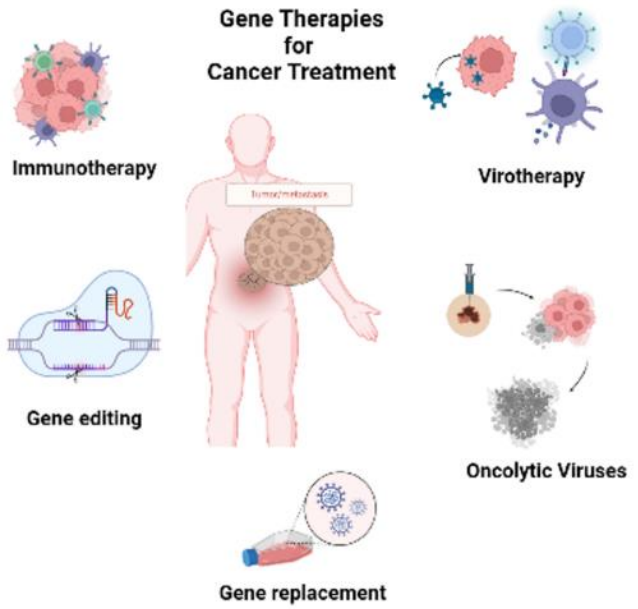

Figure 2. *Gene Therapy for cancer Treatment.*

Possibilities to interfere with oncogenic pathways and boost tumor suppressor functions are made possible by gene editing. It may be possible to slow the development of cancer by treating mutations in genes like TP53 and KRAS. CRISPR-Cas9 gene editing has been used to fix faulty BRCA1/2 genes, which can prevent hereditary breast and ovarian cancer. Furthermore, blocking immune checkpoint genes like PD-1 has demonstrated encouraging results in improving anti-tumor immune responses [34]. Figure 2 depict Gene therapy for cancer Treatment

2.4. Gene Replacement Therapy

The goal of gene replacement therapy is to restore normal cellular function by inserting functional copies of defective or absent genes into affected cells. This method depends on the introduction of foreign DNA using either viral or non-viral vectors. The efficient delivery and integration of foreign genes into the host genome is made possible by viral vectors like retroviruses, lentiviruses, and adenoviruses. Electroporation and nanoparticle-based administration are two non-viral technologies that provide safer options with lower immunogenicity [35].

The effective treatment of X-linked severe combined immunodeficiency (X-SCID) is a prime example of the potential of gene replacement therapy. Immune system reconstitution was achieved through the groundbreaking work of Cavazzana-Calvo and colleagues, who used a gamma-retroviral vector to insert a functional IL2RG gene into hematopoietic stem cells. The therapeutic viability of gene replacement is further supported by the approval of Luxturna, an AAV vector-based treatment for hereditary retinal degenerat [36]. These advances shed light on the power of gene replacement procedures to treat genetic defects and offer hope for their application to cancer treatment.

2.5. Oncolytic Viruses

Natural or synthetic oncolytic viruses selectively proliferate inside cancer cells and kill those cells. Therapeutic transgenes can be loaded onto these viruses to boost their anti-tumor abilities. Tumor cells are infected, the virus replicates, immunogenic cell death is induced, and anti-tumor immunity is activated; this is their mode of action. Oncolytic viruses provide a novel strategy for cancer treatment due to their innate tumor selectivity [37, 38].

As an example of the clinical promise of this strategy, T-VEC (Talimogene laherparepvec) was approved for the treatment of metastatic melanoma. As synthetic biology has progressed, novel oncolytic viruses with improved tumor selectivity and safety profiles have been designed. The synergistic benefits of these medicines have been further demonstrated in clinical trials that combine oncolytic viruses with immune checkpoint inhibitors [39, 40].

3. Conclusions

Over the past 30 years, gene therapy has made considerable advances towards treating cancer, with a small number of authorized medications and many more in testing. Gene therapy for cancer has more acceptable side effects and a lower risk of severe side effects than chemotherapy. Selecting the best patients for gene therapy will be easier in the future thanks to advances in tumor genome analysis and the evaluation of host humoral and cellular immune responses. Recent advances in understanding nuclease activity and creating safer gene delivery vectors will help pave the way for genome editing to be used as a novel therapy option for currently incurable diseases like cancer. Therefore, in the future, cancer prevention and management will benefit from the use of gene therapy medications that employ safe carriers and cutting-edge science.

Abbreviations

T-Vec	Talimogene Laherparepvec
DNA	Deoxyribonucleic Acid
CARs	Chimeric Antigen Receptors
X-SCID	Immunodeficiency

Author Contributions

Muhammad Haider Amin is the sole author. The author read and approved the final manuscript.

Data Availability Statement

Not applicable.

Conflicts of Interest

The author declares no conflicts of interest.

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Biography

Muhammad Haider Amin being the youngest Editor in Chief in Pakistan, Chairman Board of Governors, The University of Faisalabad, Member, Pakistan Kidney and Liver Institute (PKLI), He is deeply committed to the mission of pursuing excellence in education & research. His contribution in encouraging youth for lead. His contribution in encouraging youth for leadership and innovation are well known. He is serving the humanity on health and education and playing his role as chairman of Madinah Foundation where their mission is to reduce unemployment and poverty. He has run important positions in both corporate and governmental level. Moreover, he has received business excellence award from President of Pakistan in 2016 as well as 2019. Furthermore, has launched Global Shapers Hub an initiative of World Economic Forum working on Sustainable Development Goals.

Research Field

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