# GENE THERAPY USED IN CANCER TREATMENT

**Abstract**

Gene therapy is an advanced method to fight various diseases. It involves replacing defective genes with healthy, functional copies of those genes and may be more beneficial than chemotherapy in cancer treatment due to greater selectivity and reduced risk of non-toxicity. specific. Although there have been significant advances in preclinical studies related to improved targeting and expression in tumors, several obstacles remain that hinder success at the clinical level, including include nonspecific manifestations, low delivery efficiency, and biosafety issues. To address these challenges, innovative methods have been developed to regenerate vectors/ transgenes to create them secure and more viable. Various strategies have also been used to treat cancer, such as anti-angiogenic therapy, prodrug-activated suicide gene therapy, oncolytic virus therapy, gene therapy which is based on immunomodulation, Genetic manipulation of tumor invasion and apoptotic pathways, correction/compensation of genetic defects and RNAi Strategies . Gene therapy can target many different types of cancer including brain, lung, liver, breast, colorectal, cervical/prostate/bladder/head and neck/skin/ovary/kidney cancers. In this chapter, the latest advances in gene therapy are discussed in general and their effects on both preclinical and clinical levels and highlights various aspects related to gene delivery methods, viral/non-viral vectors used.

**Keywords:** Cancer,Gene Therapy, Viral Vectors,and Non-Viral Vectors.

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## I. INTRODUCTION

Cancer is a primary worldwide health problem that causes greater than 8 million deaths global every year. It is a multifaceted and complex disease with genomic changes influenced by host and environment interactions [1]. The past decade has seen significant advances in molecular biology, virology, genetics, immunology, and tumor biology. In 1990, Fearon and Vogelstein published a model linking genetic variation to specific defects. This has caused the improvement of cancer treatments based on mutation of tumor suppressors and inactivation of oncogenes [2]. The goal of gene therapy is to deliver genetic material to target cells or tissues for therapeutic effect. Compared to traditional therapies, it offers many advantages because it can be administered topically without the risk of systemic side effects at high therapeutic doses. In addition, most gene therapies require only one application, making them cost-effective in the long term; Presently, gene transfer era is needed for cancer remedy [3].

1. **Cancer - A Complex Genetic Disorder :** "Cancer" is a word derived from the Latin word meaning "crab". The Greek word oncos, meaning swelling, gave rise to the terms oncology and oncologist. It has been assumed that cancer arises from single cells that undergo transformation under the influence of various environmental elements , including physical agents, chemical agents, and viruses. Hundreds of genetic changes are required for ordinary cells to turn into cancer cells. The main useful mutations that lead to these transformations are mainly associated with the activation of oncogenes or the inactivation of tumor suppressor genes [1,4].

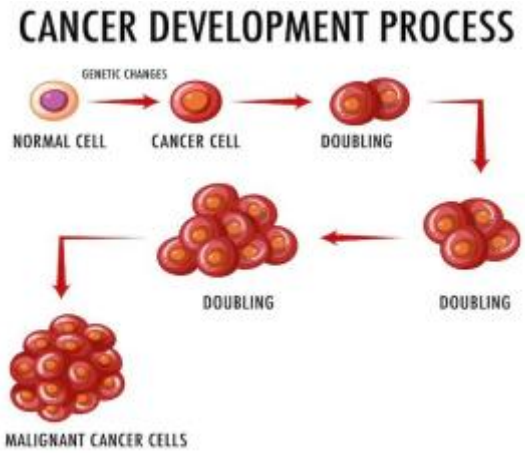


**Figure 1:** Cancer Development Process

## II. GENE THERAPY FOR CANCER: AN OVERVIEW

Gene therapy is an modern treatment approach that uses genes or short oligonucleotide sequences as agents instead of traditional drug compounds. It involves introducing one or more foreign genes into an organism to address hereditary or acquired genetic defects. Gene therapy may be categorized into two types: Somatic Cell Therapy and Germline gene therapy. By expressing the inserted DNA through cellular machinery, the disease can be treated with minimal toxicity. A pioneer in the field, Rogers and colleagues provided the first proof of concept for virus-mediated gene transfer, showing that viruses may

 

be used to introduce foreign genetic material into target cells. Inspired by these results, he went ahead and experimented on humans, becoming the first to conduct clinical trials of human gene therapy.[5]

In 1989, the US Food and Drug Administration (FDA) permitted the primary gene therapy protocol, which was changed and soon implemented. The following year a clinical trial with therapeutic intent began in cancer patients, among these, patients with advanced cancer have been treated ex vivo with genetically changed tumor infiltrating lymphocytes expressing tumor necrosis factor [6]

The research of Klein and his colleagues reached another milestone in the history of gene therapy without obtaining consent from the University of California, Los Angeles, Institutional Review Board (UCLA). Cline treated thalassemia patients by removing their bone marrow and replacing them with ex vivo plasmids containing the human globulin gene; This case shows how little knowledge about human gene therapy can make the work difficult and challenging. [7] [8]

Successful cancer treatment via gene therapy requires several prerequisites such as appropriate targets for replacement/modification, proper carriers for reaching targeted cells with sufficient expression levels of therapeutic genes while also ensuring strong efficacy safety [3][9].

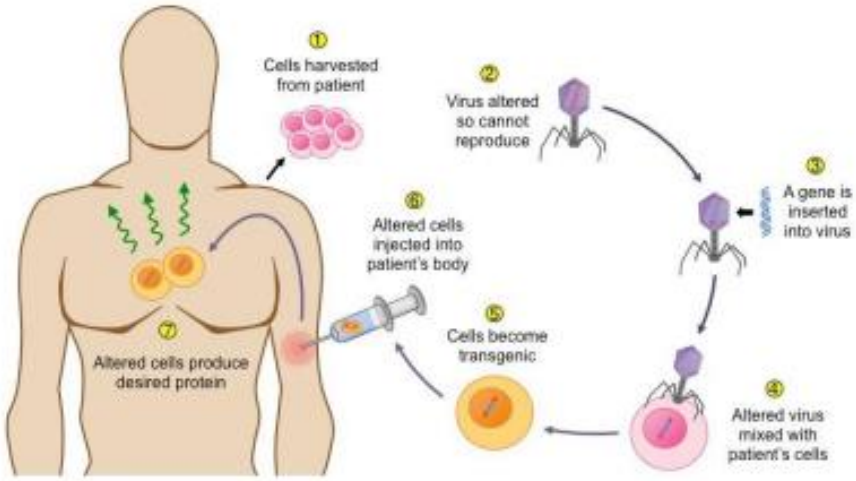


**Figure 2:** Gene Therapy

## III. GENE TRANSFER METHODS AND VECTORS USED FOR GENE THERAPY

The goal of gene therapy is to deliver the proper genetic material to the target cell or tissue and control gene expression at the appropriate time. Genetic material can be delivered to target cells or tissues using a variety of delivery methods .We can divide them according to the principle , such as (1) physical, (2) viral, (3) non-viral, (4) bacterial or yeast. Examples of physical methods used include ultrasound, microinjection, electrophoresis, and gene gun delivery. Examples of chemical methods used are lipofection, finishing, use of detergent mixtures.

 

As the name suggests, viral vectors use biological vectors (ie, viruses) as vehicles to deliver genetic material into cells, while minimal gene transfer methods use synthetic vectors (liposomes or nanoparticles). Distinctive vectors have specific characteristics according to their transduction efficiency and the efficiency of expression of the inserted genes.

Currently, viral vectors are taken into consideration to be the maximum efficient gene transfer approach to promote gene transfer [ 10 ]. However, most viral vectors have a natural affinity for precise cell types or tissues that can be used in healing processes [11].

1. **Viral Vectors :** Viral vectors can be classified into integral and non-integral vectors depends on their origin. Nonintegrating vectors such as adenoviruses and baculoviruses do not have the ability to integrate their genomes (and thus transgenes) into the host genome. Lenti, retroviruses, and adenoviruses are examples of integrative vectors that have the ability to integrate into the host genome. Transgene expression is transient and declines within weeks if the viral vector is not integrated, whereas vector integration usually results in long-term effects of months or even years. Genome integration of these transgene recipients raises concerns about the safety of these agents. Therefore, random integration with active expression sites (eg, insertional mutagenesis) has been reported [12-14].

   **Examples of Viral Vectors**

   - Retrovirus vector
   - Adenovirus vector
   - Adeno associated virus vector
   - Herpes simplex virus vector
   - Lentivirus vector

| | ADENOVIRUS | AAV | γ-RETROVIRUS | LENTIVIRUS |
|---|---|---|---|---|
| SIZE | ~90-100 nm | ~25 nm | ~80-100 nm | ~80-100 nm |
| GENOME | dsDNA | ssDNA | ssRNA | ssRNA |
| PACKAGING CAPACITY | ~8 kb – 36 kb | ~4.7 kb | 10 kb | 8 kb |
| TRANSDUCTION | Dividing and non-dividing cells | Dividing and non-dividing cells | Dividing cells | Dividing and non-dividing cells |
| TRANSDUCTION EFFICIENCY | High | Moderate | Moderate | Moderate |
| INTEGRATION | Non-integrating | Non-integrating | Integrating | Integrating |
| EXPRESSION | Transient | Transient or stable | Stable | Stable |
| BIOSAFETY LEVEL | BSL-2 | BSL-1 | BSL-2 | BSL-2 |
| IMMUNOGENICITY | High | Low | Moderate-High | Moderate-High |
| GENE THERAPY STRATEGY | *In vivo* | *In vivo* | *Ex vivo* | *Ex vivo* |

**Figure 3:** Viral Vectors

- **Adenovirus Vector:** Adenoviruses are the most generally used vectors in cancer treatment. There are at least 51 serotypes in this family of genomic DNA viruses. Of these, serotypes 2 and 5 are most generally used in gene therapy. This virus often causes respiratory diseases, especially in the upper respiratory tract [15]. Also,

 

many of these vesicles (endosomes) degrade in the cytoplasm, leaving free viral particles, but can cause gastroenteritis, conjunctivitis, or cystitis. The particles are quickly moves towards the cellular nucleus, leaving only DNA and a few proteins behind. Once in a while, the adenovirus DNA starts to replicate. Adenoviral gene therapy vectors will initiate the process that leads to the production of therapeutic proteins. Since the DNA of this virus does not combine into the chromosomes of the cell, its activity is temporary (usually a few weeks) [16, 17].

Adenovirus can infect many types of cells, whether they are dividing cells or not. This makes them suitable for use in the treatment of cancer, as they may be used in various types of cancer, regardless of the origin or the initial growth rate. Adenoviruses without problems penetrate epithelia, making them perfect for treating carcinomas. then again, adenoviral vectors are rarely used in tumors of hematopoietic origin due to the fact they may be tough to introduce into most people of hematopoietic cells [18].

2. **Non-viral Vectors:** Non-viral gene transport structures are presently the subject of lots studies as an alternative to gene delivery structures. The most effective shape of non-viral system is naked plasmid DNA and its benefit is ,it has the lowest form of toxicity or side effects. additionally, it is simple to construct and cheaper to manufacture. but, its drawback is that the gene transfer efficiency is low in comparison to virus-mediated gene transfer [19]. Accordingly, to improve cationic polymers, metabolic performance or lipid formulations were evolved to concentrate plasmid DNA to defend DNA degradation and improve plasmid uptake and metabolism [19]. The benefit of these formulations is that the polymer or lipid may be modified particularly without difficulty to gain positive properties. Unfortunately, the fulfillment of nonviral transport structures in clinical programs in gene therapy is limited [20].

The fulfillment of non-viral gene therapy depends on severa intracellular and extracellular obstacles that have an effect on the performance of all gene transport systems, which includes cellular uptake, contact break out sensation, nuclear uptake and gene expression [20-22].

## IV. GENE THERAPY FOR CANCER TREATMENT

Cancer is because of disruption of regular cellular proliferation and apoptosis. Advances in cancer gene therapy require new therapeutic agents with novel modes of action, a couple of cellular killing mechanisms, and synergy with conventional therapies. Several gene therapy techniques were evolved for the control of ovarian most cancers, which includes autologous gene therapy, immunotherapy, anti-angiogenic gene therapy, siRNA therapy, proapoptotic gene therapy , oncolytic virus therapy, and enzyme-targeted gene therapy (23). As of November 2017, more than 2,597 gene therapy clinical trials were conducted global. Greater than 65 % of those trials are associated with cancer, accompanied by cardiovascular sicknesses and monogenic sicknesses [24]. Using car T-cell therapy has shown significant outcomes in the control of myeloid and lymphocytic leukemia. As of August 2019, only 22 gene products had been accepted to deal with various problems. Most of the gene products used inside the treatment of numerous cancers are listed into table 1 [24].

 

**Table 1: Gene Therapies Products Approved for Therapeutic Use**

| Trade Name (Proper Name) | Data of approval and Approving Agency | Vector and Modified Gene | Indication | Route of Administration |
|---|---|---|---|---|
| Gendicine | 2003 State Food and Drug Administrati on of China | Adenovir al vector P53 | Head and neck squamous cell carcinoma | In vivo |
| Imlygic (talimogene laherparepvec, T-vec) | 2015 FDA | GM-CSF HSV –I | Melanoma | In vivo |
| Kymriah ™ (tisagenlecleucel) | August 2017 FDA | CD19-specific CAR T Lentiviral vector | Acute lymphoblastic leukemia | Ex vivo |
| Oncorine (Recombinant Human Adenovirus Type 5 Injection) | 2005 State Food and Drug Administration of China | Adenovirus Type 5 | Head and neck and esophagus cancer, Nasopharyng eal cancer, etc | In vivo |
| Yesterday™ (axicabtagene ciloleucel) | October 2017 FDA | CD 19 - specific CAR T Y Retroviral vector | Non-Hodgkin lymphoma | Ex vivo |

1. **Chimeric Antigen Receptor (CAR) T-Cell Therapy:** The first CAR T cell therapy accepted through the U.S. Food and Drug administration (FDA) in August 2017 is tisagenlucucel. Another CAR T-cell therapy accepted by the US FDA in October 2017 to treat affected adult person with relapsed or refractory large B-cell lymphoma after two or more systemic therapies, which includes second-line DLBCL. The targeted axicabtagene/ciloleucel , box large B-cellular lymphoma, high-grade B-cell lymphoma, follicular lymphoma DLBCL. The National Institutes of Health Clinical Trials Registry includes several ongoing clinical trials of CAR T cell therapy for a spread of diseases, consisting of multiple myeloma, central nervous system tumors, hepatocellular carcinoma, and lung cancer [25, 26, 27, 28].

Chimeric antigen receptors (CARs) are complicated receptors for antigens that modulate the specificity and feature of T lymphocytes and/or other immune cells inside a

 

cell. The concept behind the use of CARs in tumor immunotherapy is that CARs engineered to target tumor-related antigens may be replicated fast and uniformly. Direct injection of T cells that focus on those armed tumors bypasses the barriers and dynamics of active immunity. In comparison to conventional passive immunization with live antibodies, supraphysiological CAR-modified T cells act as active agents that interact with tumor-related antigens, resulting in immediate and long-term antibody effects [29, 30].

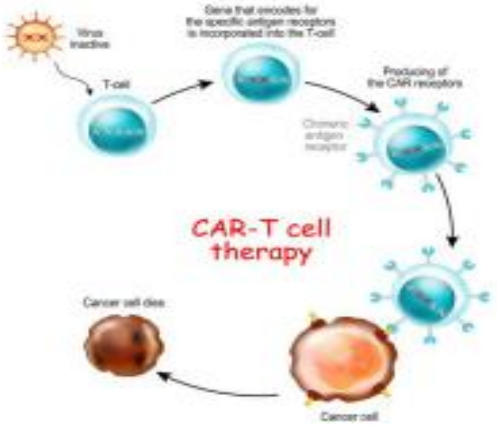


**Figure 4:** CAR T Cell Therapy

- **Yescarta (Axicabtagene Ciloleucel):** Kymriah is the first CAR T-cell-based gene product accepted through the FDA for the treatment of B-cell acute lymphoblastic leukemia [31]. This is the second CAR T-cell therapy used to treat competitive non-Hodgkin's lymphoma. These are CD19 antigen-particular ex vivo changed autologous T cells infected with a gamma retrovirus. It encodes a CAR containing a murine extracellular anti-CD19 single stranded variable fragment fused to the cytoplasmic domain of CD28 and CD3 zeta-aggregation domain [32,33].

2. **Anti-Tumor Angiogenesis:** Tumor based angiogenesis involves various growth factors, which includes vascular endothelial growth factor (VEGF), fibroblast growth factor-2 (FGF-2), angiopoietin or IL-eight, which give oxygen and nutrient supply. There are two methods to inhibit tumor angiogenesis. The first method is to reduce the expression of pro-angiogenic factors which includes VEGF and the second method is to up-alter the expression of anti-angiogenic factors which include angiostatin, endostatin and human soluble FMS-like tyrosine kinase receptor. In spite of a successful therapeutic use of mAbs including bevacizumab for targeted cancer treatment, production and administration of therapeutic mAb is restricted because of expensive manufacturing. Consequently , gene-primarily based research have been performed to develop angiogenesis-targeted cancer therapies [34,35].

3. **Oncolytic Virotherapy:** Oncolytic virus therapy (OV) is the simplest way to treat cancer. OVs use replication capable viruses that may selectively multiply in tumor cells. Oncolytic viruses are categorized as common viruses, including parvovirus and Newcastle disease, that may selectively replicate in tumor cells without the need for

 

genetic changes. Other groups of viruses, which includes vesicular stomatitis virus, adenovirus, herpes simplex virus (HSV), and herpes simplex virus, were genetically modified to enhance immunity and cancer and decrease pathogenicity. Oncolytic virus therapy in the treatment of cancer is an immune-mediated therapy. Oncolytic viruses act by way of directly lysing tumor cells and introducing wild-type tumor suppressor genes [36,37]. Changes in p53 gene characteristic occur in half of malignancies, and broad-spectrum p53 gene induction restores normal p53 expression. Several p53-expressing recombinant OVs were developed with the purpose of manufacturing more effective OVs that cooperate with host immunity or other tumor cell killing therapies [37, 38].

- **Oncorine (rAd5-H101):** That is the primary oncolytic recombinant Ad5 (rAd5-H101) accepted for the remedy of refractory nasopharyngeal cancer. Decreased p53 quality is related to drug resistance and decreased survival in patient with non-small cell lung cancer [38]. Oncorin is an Ad5 virus with a deletion inside the E1B 55K quality. Inactivation of p53 quality inside cells is important to prevent wild-type initiation of the apoptotic pathway. Abolishing the E1B 55K quality prevents the infection from replicating in normal cells and, so to speak, allows replication in p-53-deficient cells. In tumor cells, viral replication causes oncolysis, providing a means of treatment for severe tumors. After Lydia's cancer cell, adenovirus is released and contaminates another cell, resulting in extreme oncorin-mediated cell death [39, 40].

## V. CONCLUSION

Gene therapy is a new option in the treating diseases for which traditional treatments are not yet satisfactory. Gene therapy for cancer has made great strides over the past 30 years, but only a few drugs have been approved and others are still in the experimental phase. In cancer therapy, gene therapy is relatively safer than chemotherapy and its side effects are more tolerable.Vectors are beneficial for extremely particular varieties of cancer and patients, and although they do not but provide a treatment, they have got improved and keep to enhance the quality of life for patients. This type of treatment seems to be a suitable method to fight against malignant tumors. The successful use of T lymphocytes integrated with autologous and allogeneic chimeric antigen receptors in the administration of adoptive immunotherapy has improved safety and effectiveness of gene therapy. In the future, gene therapy using safe vectors and advanced biotechnology will be even more important in cancer prevention.

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