**Gene Therapy Used in Cancer Treatment**

**Vrushali S. Shinde1, Sachin B. Somwanshi2 & Kiran B. Kotade3**

1. Research Scholar, Department of Pharmaceutics, PRES’s, College of Pharmacy (For Women), Chincholi, Nashik, MH, India-422102

E-mail: vrushalis681@gmail.com

1. Associate Professor, Department of Pharmaceutics, PRES’s, College of Pharmacy (For Women), Chincholi, Nashik, MH, India-422102

E-mail: sachinsomwanshi27@gmail.com

1. Associate Professor, Department of Pharmacology, PRES’s, College of Pharmacy (For Women), Chincholi, Nashik, MH, India-422102

E-mail: kirankotade@gmail.com

**Abstract**

Gene therapy is a new tool used in combating different diseases. Gene therapy in which involves replacement of a defective gene with a functional, healthy copy of that gene and it is a potentially beneficial for cancer treatment approach particularly over chemotherapy, which often lacks selectivity and may cause non-specific toxicity. Despite significant process preclinically with respect to both enhanced targeting and expression in a tumors selective manner several hurdles still prevent success in the clinical, including non-specific expression, low efficiency delivery and biosafety. There are various innovative approaches for the development to reconstruct vectors / transgender to make the safer and more effective. There are different strategies have been employed for the cancer, such as antiangiogenic therapy, prodrug activating suicide gene therapy, oncolytic virotherapy, Gene therapy based immune modulation, genetic manipulation of apoptic and tumour invasion pathways, antisense, correction /compensation of gene defects, and RNAi strategies. Cancer types in which gene therapy targeted such as brain, lung, liver, breast, colorectal,head, prostate, bladder, and neck, skin, ovarian and renal cancer. This review discusses recent advances in general therapy and their impact on preclinical and clinical level and also discusses highlights of gene therapy.

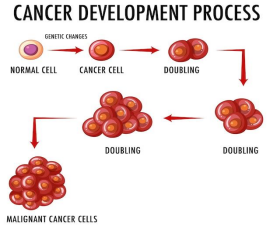
**Keywords**: *Gene therapy, Gene delivery, Cancer, Viral vectors, Non-viral vectors*

**I. INTRODUCTION**

Cancer is a major global health problem accounting annually, for more than eight million deaths globally. It is a complex, multifunctional disease in which involves changes in the genome, which is orchestrated by host and environmental interactions[1]. The past decade has been witness to numerous advances in the molecular biology, virology, genetics, immunology and tumor biology. In 1990, Fearon and Vogelstein proposed a model which linked with a malignant transformation to a combination of specific genetic errors this contributed to the development of cancer gene therapy strategies which is based on replacement of defective tumour suppressor gene and inactivation of oncogens [2]. The aim of gene therapy is that delivering genetic material into target cells or tissues and to express it with intention to gain therapeutic effect. It has the more advantages as compared to conventional therapies due to the fact that it can be administered locally, thereby delivering, locally, a high therapeutic dose without risking any systemic adverse effects. Furtermore, since most gene therapies are the single time applications which can be cost effective in the long run. Current gene transfer technology is suitable for cancer gene therapy [3].

* 1. **Cancer – Complex Genetic Disease**

The word “cancer” comes from the Latin word for crab. The Greek word oncos means swelling and where we get the word oncology or oncologist. As long been suggested that the cancer has evolved from a single cell transformed by the influence of the environmental factors such as physical, chemical factors and viruses. Changes occur in the hundreds of genes, so called mutations, are required to transform a normal cell into a cancer cell. The major functional changes which transform a cell are mainly the activation of oncogens or inactivation of tumor suppressor genes [1,4].



**Figure No.1: Cancer Development Process**

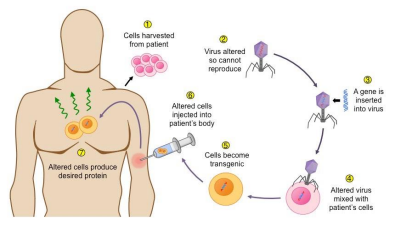
**II. GENE THERAPY FOR CANCER: AN OVERVIEW**

Gene Therapy is a novel treatment method which utilizes genes or short oligonucleotide sequences as therapeutic molecules, instead of conventional drug compounds. It involves the introduction of one or more foreign genes into an organism to treat hereditary or acquired genetic defects. There are two types of gene therapy such as Somatic Cell Therapy and Germline gene therapy. The disease is treated with minimal toxicity, by the expression of the inserted DNA by the cell machinery. Rogers et al. was one of the first to demonstrate an initial proof of concept of virus mediated gene transfer. And he was showed that foreign genetic material can be transferred to cells of interest by utilizing viruses. Motivated by the results he went even further and tested in humans. Because of this experiment, Rogers became the first to perform a human gene therapy trial [5].

The US Food and Drug Administration (FDA) approved the first gene therapy protocol, and it was carried out in 1989.The first clinical trial on cancer with an therapeutic intend was started in the following year, wherein patients with advanced melanoma were treated with tumor infiltrating lymphocytes genetically modified ex-vivo to express tumor necrosis factor [6].

Another important milestone in the history of gene therapy was the study conducted by Cline et al. The reason behind this study presents a milestone in the history of gene therapy, was that the study was done without the consent to perform these studies from the University of California, Los Angeles (UCLA) Institutional Review Board. Cline treated thalassaemia patients, in that he extracted bone marrow cells from these patients and transfected ex vivo with plasmids containing the human globulin gene. This case demonstrated that knowledge was very limited and that human gene therapy would be technically, as well as ethically much more complex than expected [7,8].

There are some prerequisites for a successful gene therapy treatment in cancer, such as suitable target to be replaced or modified, a carrier to reach interest of gene to the cell, a successful targeting of the vector, and a sufficient expression of the therapeutic genes in the target cells. Besides, a strong therapeutic efficacy safety is also mandatory for the success of the treatment [3,9].

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**Figure No. 2: Gene Therapy**

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

In the gene therapy the challenge is that to deliver an adequate amount of genetic material into target cells or tissues and to maintain gene expression for a desired period of time. Genetic material can be introduced to their target cells or tissues via different methods of delivery. On the basis of principle we can classified them into (1) Physical, (2) Viral, (3) Non-viral, (4) Bacterial or yeast. Ultrasound, Microinjection, Electrporation and gene gun deliveries are examples of physical methods that have been used. Lipofection, perfection, using detergent mixtures deliveries are example of chemical methods that have been used.

As the name already implies that, with viral vectors a biological (I. e. Virus) vector is used as a vehicle to deliver the genetic material into the cells, whereas with minimal gene transfer methods a synthetic carrier (liposomes or nanoparticles) is used. Different vectors have different properties in relation to their transduction efficiency and their efficacy to express the introduced genes.

Currently viral vectors are considered as the most effective for all gene delivery method for inviting gene transfer[10]. Most viral vectors have, however, already natural tropism to certain cell types or tissues, which can be utilized for therapeutic approaches [11].

**3.1. Viral Vectors**

On the basis of origin viral vectors can be divided into integrating and non integrating vectors. Non integrating vectors such as Adenoviruses and baculoviruses Which have lack the ability to integrate their genome ( and, hence, with it also the transgene) into the host genome. Lenti, retroviruses, Adeno associated viruses are the examples of integrating vectors which have ability to integrate into the host genome .While the expression of the transgene is transient in case of non integrating viral vectors that is diminishing in a few weeks, integrating vectors commonly results in long term expression that is months, up to years. This integration of the transgene into the host genome has raised concerns about the safety of these factors .Due to this fact that integration has been observed with terrorists vectors to occur occasionally in actively expressed sites (I. e. Insertional mutagenesis) [12-14].

**Examples of viral vectors**

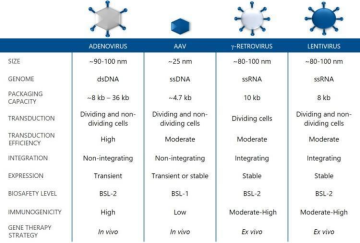
a. Retrovirus vector

b. Adenovirus vector

c. Adeno associated virus vector

d. Herpes simplex virus vector

e. Lentivirus vector



**Figure No. 3: Viral Vectors**

**3.1.1. Adenovirus Vector**

The most widely used vectors in gene therapy against cancer are Adenoviruses. They make up a DNA genome virus family of at least 51 different serotypes. Of those, the serotypes 2 and 5 are the most commonly used ones in gene therapy. These viruses commonly cause disease of the respiratory tract, primarily the upper tract [15]. They may also cause gastroenteritis, conjunctivitis or cystitis, although the majority of these vesicles (endosomes) are degraded in the cytoplasm leaving the viral particles in a free state. The particles are quickly transported toward the nucleus where the only the DNA and a few proteins pass into its interior. Once inside the nucleus, the adenoviral DNA begins to to replicate. A gene therapy adenoviral vector will begin its activity of initiating the processes that culminate in therapeutic protein production. The DNA of these viruses does not integrate into the cellular chromosomes and so its activity is transitory (generally weeks) [16, 17].

Adenoviruses can infect large variety of cellular types whether or not they are in active cellular division. This makes their use in gene therapy against cancer advantageous since they can be used in many different neoplasms regardless of their primary origin or the velocity of their growth. Adenovirus are easily introduced into epithelium which makes them ideal for treating carcinomas. On the other hand, adenoviral vectors are not very useful in neoplasms of hematopoietic origin because it is difficult to introduce them into the majority of hematopoietic cells [18].

**3.2. Non-viral Vectors**

Non-viral gene delivery systems are a topic which is currently being studied extensively as alternatives for viral delivery systems. The simplest form of a non-viral system is naked plasmid DNA, and advantage of this is that it poses the lowest form of toxicity or other unwanted reactions. And also, it is easy to formulate and inexpensive to produce. However, its disadvantage is the low transfection efficiency compared to viral-mediated gene transfer [19]. As a result, to improve cationic polymers, transfection efficiency, or lipids formulations have been developed to condense plasmids DNA to protect the degradation of DNA and to enhance uptake and transfection of plasmids [19]. The advantage with those formulation is that polymers or lipids can comparatively easily be design to attain certain properties. Unfortunately, the success of non-viral delivery systems in clinical applications in gene therapy has been limited [20].

The success of the non-viral gene therapy is depends on the various extra and extracellular barriers which affect the efficacy of all gene delivery systems, including cellular uptake, emotional escape, nuclear uptake, and gene expression [20-22].

**IV. GENE THERAPY FOR CANCER TREATMENT**

Cancer occurs because of disrupting the normal cell proliferation and apoptosis process. Advances in cancer gene therapy need a novel therapeutic agent with novel mode of action, several mechanisms of cell death, and synergy with conventional management. Several gene therapy approaches were developed for the management of cancer, including suicide gene therapy, immunotherapy, antiangiogenic gene therapy, siRNA therapy, proapoptotic gene therapy, oncolytic virotherapy, and gene directed enzyme prodrug therapy [23]. In November 2017, greater than 2597 clinical trials were conducted on gene therapy in the world. Among these trials, greater than 65% are associated with cancer, followed by cardiovascular and monogenetic diseases [24]. The use of CAR T cell therapy showed significant results for the management of both myeloid and lymphoid leukemia. Until August 2019, only 22 gene products were approved for the treatment of different disorders. Most gene products used in treatment of variety types of cancers as shown in Table 1 [24].

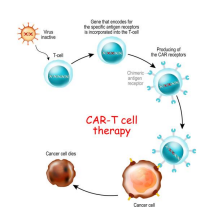
**Table No. 1**: Gene Therapies Products Approved for Therapeutic Use

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **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 TM  (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 |
| YesterdayTM  (axicabtagene ciloleucel) | October  2017 FDA | CD 19 - specific  CAR T Y Retroviral vector | Non-Hodgkin lymphoma | Ex vivo |

**4.1. Chimeric Antigen Receptor (CAR) T-Cell Therapy**

The First United States Food and Drug Administration (FDA) approved CAR-T cell treatment, in August 2017, is tisagenlecleucel. The second U. S. FDA approved CAR-T cell treatment, in October 2017, is axicabtagene ciloleucel which is indicated for the treatment of adult patients with relapsed or refractory large B cell lymphoma after two or more lines of systemic therapy including DLBCL not otherwise specified primary mediastinal large B cell lymphoma, high grade B cell lymphoma and DLBCL arising from follicular lymphoma.According to U. S National Institute of Health clinical trial registration includes multiple clinical trials are currently going on with CAR-T cell treatment for different mignacies including multiple myeloma, CNS Tumor, hepatocellular carcinoma, lung cancer [25,26,27,28].

Chimeric antigen receptors (CARs) are recombinant receptors for antigens which redirect the specificity and function of T lymphocytes and /or other immune cells in a single molecule. The concept of using CARs in cancer immunotherapy is that CARs, which are programmed targeting tumor-associated antigens, can be replicated rapidly and homogenously. Direct infusion of these armed tumor targeting T-cells bypass the barriers and kinetics of active immunization. Unlike general passive immunization using direct antibody, CAR modified T-cell with supraphysiologic activities work as an active medication, interacting with tumor-associated antigens which resulting in both immediate and long term effects of anti-neoplasm [29,30].



**Figure No. 4: CAR T Cell Therapy**

**4.1.1. Yescarta (Axicabtagene Ciloleucel)**

Kymriah is the first FDA approved CAR T-cell based gene product to treat replased B-cell acute lymphoblastic leukemia [31]. It is another CAR T-cell therapy used for the management of aggressive Non Hodgkin lymphoma. It is CD19 aantige-specific exvivo modified autologous T cells infected with a gamma -retroviral. It encodes a CAR comprising an extracellular murine anti- CD19 single -chain variable fragment fused to a cytoplasmic domain that possesses CD28 and CD3-zeta co-stumularory domains [32,33].

**4.2. Anti-Tumor Angiogenesis**

Tumor-driven angiogenesis several growth factors are involved, such as vascular endothelial growth factor (VEGF), fibroblast growth factor -2 (FGF-2),angiopoietins or IL-8,to secure oxygen and nutrients supply. Two approaches are being pursued to block tumor angiogenesis. The first approach is down -regulation of pro-angiogenic factors expression, such as VEGF, and the second approach is up-regulation of expression of antiangiogenic factors such as angiostatin, endostatin, and human soluble FMS-like tyrosine kinase receptor. Despite the successful therapeutic use of mAb like Bevacizumab for targeted therapy of cancer, the production and administration of therapeutic mAb are limited due to costly production. Therefore, gene-based studies were done to develop an angiogenesis - targeted cancer treatment [34,35].

**4.3. Oncolytic Virotherapy**

Oncolytic virotherapy (OV) is the most promising approach for tumor immunotherapy. OV uses replication -competent viruses that can proliferate selectively at tumor cells. Oncolytic viruses grouped as naturally occurring viruses like parvoviruses, and Newcastle disease viruses that selectively replicate in tumor cell without genetic modification. The second virus category, such as vesicular stomatitis viruses, adenoviruses, measles viruses, herpes simplex virus (HSV) and vaccines viruses, genetically modified to improve the safety, tumor specificity, and decrease virus pathogenicity. The therapeutic use of oncolytic viruses for cancer treatment is an immune related treatment alternative. Oncolytic viruses act by direct lyses tumor cells and by introducing wild type tumor suppressor gene [36,37]. Change in p53 gene function is present in half of all malignancies, and the induction of wide type p53 gene re-establishes the normal p53 expression. Several recombinant OVs expressing p53 were developed with the aim of producing more potent OVs that act in combination with host immunity or with other treatments modality to destroy tumor cells [37,38].

**4.3.1. Oncorine (rAd5-H101)**

It is the first replicative, oncolytic recombinant ad5 (rAd5-H101) approved to treat refractory nasopharyngeal cancer. Loss of p53 gene linked with drug resistance and survival rate reduction in non-small cell cancer patients [38]. Oncorine is an ad5 virus with a deletion in the E1B 55K gene. Host cell p53 gene inactivation is essential for wild type to block the activation of apoptic pathway. The removal of the E1B 55K gene inhibits viral proliferation in normal cells, allowing only proliferate in p-53 deficient host cells. In tumor cells, viral proliferation causes oncolysis that is the mechanism to treat solid tumors. Following cancer cell Lydia, adenoviruses release and infect another cell activating a serious of Oncorine mediated cell death [39,40].

**V. CONCLUSION**

Gene therapy represents a novel alternative for the management of diseases of that have no satisfactory cure. Gene therapy for cancer treatment has good progress in the last three decades, few drugs approved, while others are still in trials. Relatively gene therapy has better safety with tolerable adverse effects than chemotherapy for the treatment of cancer. Vectors are useful in very specific cancers and patients and although they do not yet provide a cure, they do improve patient quality of life and will continue to do so more and more. This type of therapy seems to be an adequate path to follow to successfully fight malignant tumors. The success of using autologous and allogenic chimeric antigen receptor integrated T-lymphocytes in mediating adoptive immunotherapy enhances the safety and effectiveness of gene therapy. Gene therapy drugs with safe vectors and advanced biotechnologies would play a greater role in the prophylaxis management of cancer in the future.

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