

# Gene Therapy and Its Application in Breast Cancer Treatment

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**Abstract.** As a new medical field, gene therapy has shown great potential in cancer treatment. This article reviews the principle, mechanism and application of gene therapy in the treatment of breast cancer, and discusses the prospect and challenge of its future development. Mutation, as the common cause of cancer, is the target of gene therapy. By replacing disease-causing genes, suppressing malfunctioning genes, or introducing new genes, a variety of mutation caused disease could be treated... In particular, this paper presents genome editing technologies such as CRISPR-Cas9, which correct genetic differences by precisely modifying existing DNA within cells. Finally, this paper discusses the future development of gene therapy, including its application in multiple cancer models, and the safety challenges faced. Despite some serious problems, such as immune responses and non-specific targeting, the potential of gene therapy is still huge. As technology continues to advance, we expect gene therapy to revolutionize cancer treatment.

**Keywords:** gene therapy; mutation; breast cancer.

## 1. Introduction

In human body, there are more than 20,000 genes that orchestrate with each other to ensure the proper work of the whole system. Among them, some gene is responsible for controlling the reproduction and division of cells, others involved in the regulation of cell death or gene repair. Once one of these genes doesn't function well, some issues might occur, including the irreversible gene damage and uncontrolled cell growth, which are all symptoms of cancer development [1]. Cancer begins when cells in the body become abnormal and begin to grow out of control. The main types of genes that play a role in cancer are: oncogenes, tumor suppressor genes, and DNA repair genes [1]. Cancer is usually the result of changes in multiple genes within cells. Genes can mutate in many different ways. The most basic type of mutation is a change in the DNA sequence in a gene. DNA is made up of four different bases, which are arranged in a specific order [2]. Mutations occur when a base changes or the order of the bases changes. Other types of genetic mutations include insertional mutations, which add an extra piece of DNA to a gene. Replication mutations occur when a part of a gene or part of a chromosome is copied one or more times. Deletion mutations are when a section of DNA is removed from a gene, an entire gene is missing, or a chromosome is broken resulting in the loss of some genetic material [3]. A translocation mutation occurs when part of one chromosome breaks off and attaches to another chromosome. Inversion mutations occur when a chromosome is broken at two points and a piece of DNA is flipped and reinserted into the chromosome.

As the cause of cancer is gene mutation, a method to repair these disruptions is fundamental for cancer cure. Nowadays, gene therapy, a molecular biology method to introduce the target gene into the body to achieve diseases treatment, has been developed [4]. Broadly speaking, the concept of gene therapy involves the transfer of genetic material into cells, tissues, or entire organs with the goal of curing a disease or at least improving the clinical condition of the patient, and is a technique to treat or cure a disease by modifying a person's genes.

Gene therapy can work through a variety of mechanisms, such as replacing disease-causing genes with healthy copies, suppressing disease-causing genes that don't function properly, or introducing new or modified genes into the body to help treat disease [5]. Later research led to advances in gene therapy technology. A newer technique called genome editing, such as CRISPR-Cas9, uses a different approach to correct genetic differences. Instead of introducing new genetic material into a cell,



genome editing introduces molecular tools to alter existing DNA in the cell. Except for the precise operation of target gene, another key factor in the success of gene therapy is the development of delivery systems that can efficiently transfer genes across a variety of tissues without causing any side effects [5]. Currently, vectors based on virus, including retroviruses, lentiviruses, adenoviruses, and adeno-associated viruses, are the best options for efficient gene delivery. Clinically, gene therapy products are being widely studied for the treatment of diseases such as cancer, genetic diseases and infectious diseases.

Breast cancer is one of the most common malignant tumors in the world. At present, there are many traditional therapies that have relatively good response to the treatment of early breast cancer [6]. However, due to the existence of metastasis, the therapeutic effect of traditional therapies for advanced cancer cannot reach the expectation. As an alternative to these traditional treatments, gene therapy can target individual gene mutations or more complex diseases. Within breast cancer patients, the most common genetic mutations appear in BRCA and HER2, which are the potential cause of breast cancer [7]. BRCA genes are tumor suppressor genes that typically play a role in preventing cancer. They regulate cell growth and division and assist in the repair of DNA damage. However, mutations in these genes can increase the risk of developing certain types of cancer. There are two known BRCA gene mutations that are associated with cancer development—BRCA1 and BRCA2. Mutations in these genes can elevate the risk for women to develop breast and ovarian cancers. Additionally, mutations in the BRCA2 gene are linked to an increased risk of breast cancer and prostate cancer in men. Furthermore, BRCA2 mutations are also associated with a slightly higher risk of pancreatic cancer in both men and women. HER2, also known as the ERBB2 gene or HER2/neu gene, stands for human epidermal growth factor receptor 2. This gene is classified as an oncogene, encoding a protein that is present on the cell surface and is involved in cell growth regulation. In most breast cancer cells, the expression level of HER2 protein is extremely high. Mutations in the HER2 gene can lead to the production of excess HER2 protein, which can stimulate uncontrolled cell growth and contribute to cancer development. Certain types of breast cancer, esophageal cancer, and gastric cancer are identified as HER2-positive due to the presence of this gene mutation [7]. The identification of HER2 status in cancer is crucial for determining appropriate treatment strategies, as HER2-targeted therapies can be effectively used in the management of HER2-positive cancers.

## **2. what is Gene therapy**

Human gene therapy aims to modify or manipulate the expression of genes or alter the biology of living cells for therapeutic use. Gene therapy is a technique that modifies a person's genes to treat or cure diseases. Gene therapy can work through a variety of mechanisms [8]:

Replace the disease-causing gene with a healthy copy (Gene Addition).

Inhibit disease-causing genes that don't function properly (Post-Transcriptional Gene Silencing).

Introducing new or modified genes into the body to help treat disease (Gene Editing).

Gene augmentation is a therapeutic approach for ailments attributed to single-gene variations. This singular intervention entails the incorporation of an operational duplicate of an absent or defective gene into an individual's cellular framework through a genetically-engineered vector, which may be viral or non-viral in nature (acting as a conveyance medium). The objective of such therapy is to enable the novel gene to synthesize a protein that the body was previously incapable of producing in sufficient quantities [1].

Gene silencing post-transcriptionally neutralizes specific messenger RNAs (mRNAs) to hinder gene expression. The mRNA of a gene intended for expression is instead subjugated (diminished). With the suppression of mRNA, the active synthesis of protein is curtailed compared to pre-silencing levels. Techniques for gene silencing are harnessed to counteract diseases such as cancer and conditions like sickle cell anemia. Gene editing represents an exacting scientific advancement designed to introduce,

eliminate, or modify discrete segments of DNA. This process involves precise incisions in the DNA at the location of dysfunction. Once the DNA is cut, the cell initiates an innate repair process.

By either disrupting deleterious genetic sequences or by integrating new sequences to rectify defective ones, gene editing facilitates lasting genetic alterations, enabling cells to resume normal functions and potentially reversing pathological states. For the efficacy of any gene therapy method, the transference of genetic material into human cells is essential, typically facilitated by engineered viral or non-viral vectors, known as "conveyance vehicles" for genetic cargo. Vectors are often modified viruses that have been disarmed of their infectious capabilities but retain their innate capacity to penetrate target cells and embed new genetic information. These vectors can be deployed via two principal methodologies—*ex vivo* (outside the body) or *in vivo* (inside the body).

*Ex vivo* gene therapy involves the application of the vector with the revised gene to a patient's cellular sample in a laboratory, followed by the reintegration of these cells into the patient. For gene editing or base editing, the editing agents may be directly introduced to cells in a lab setting, bypassing the need for a vector, to achieve a one-time genetic alteration. *In vivo* application involves the direct injection of the vector, laden with the therapeutic component such as a gene, a silencing agent, or an editing tool, into the patient's body [9].

The risks associated with gene therapy are contingent upon the specific treatment modality, the delivery system (vector), and the method of cellular delivery. These risks might encompass adverse immune responses, unintended cellular targeting leading to complications, adverse effects from the insertion of genetic material, and unintended gene activation.

### **3. How it work in breast cancer**

Breast cancer (BC) is the most common malignancy worldwide and the second leading cause of death among women, "The prevalence of BC in the United States is one in every eight women while in Asia, one in every 35 women suffers from breast cancer [9]. In Iran, there are 10 cases per 100 000 population, and 7000 new cases are reported each year"(Dastjerd,2021) and its causes include a variety of genetic and environmental factors. Therefore, effective treatment of this cancer requires new treatments. Traditional methods of treating this cancer have side effects, so a great deal of research has been conducted over the past decade to find new ways to alleviate these problems. Research into the molecular basis of breast cancer has led to gene therapy becoming an effective treatment for this cancer. Gene therapy involves delivering genetic material through a vector to a target cell and then correcting, adding or suppressing the gene. In this technique, tumor cells must be targeted without affecting normal cells. In addition, clinical trial studies have shown that this method is less toxic than traditional therapies.

Over the recent past, the pivotal influence of genetic factors in the onset of breast cancer has gained affirmation. Females possessing variations in the BRCA1 (a gene predisposing to breast cancer) and BRCA2 genes exhibit an elevated likelihood of breast cancer onset. The BRCA1 gene, inherited from both parental lines, is linked to approximately 5-10% of all breast cancer instances. It has been demonstrated through research that a conducive environmental context is essential for the manifestation of cancerous genes. Conversely, women with a history of multiple pregnancies are associated with a reduced risk of developing breast cancer when compared to those with fewer pregnancies.

Breast cancer often remains asymptomatic in its initial phases and is typically identified through the process of screening mammography. Should symptoms manifest, the most prevalent is the presence of a painless mass within the breast tissue. Other potential indicators include persistent alterations in the breast such as increased density, inflammation, or erythema, and nipple irregularities like spontaneous discharge—particularly if bloody, flaking, or accompanied by nipple retraction. This form of cancer is inherently heterogeneous, characterized by distinct phenotypic and morphological

traits, leading to a wide array of clinical presentations. Consequently, a multitude of therapeutic approaches have been devised to combat this disease [7].

These therapeutic strategies are designed with the goal of enhancing the quality of life for individuals affected. However, each approach comes with its inherent constraints. The principal challenge with these treatments is their non-specificity; they are not always efficacious. For instance, medications prescribed within these strategies are predominantly delivered intravenously, resulting in systemic drug distribution and the potential for patient toxicity. Moreover, these pharmaceuticals impact both malignant cells and healthy cellular elements within the body.

#### **4. The Future development of Gene Therapy**

The domain of gene therapy is expansive and is seen as a beacon of hope for the invention of groundbreaking treatments that have the potential to significantly impact the prevention of mortality from cancer.

Cancer gene therapy is a burgeoning area that presents a multitude of promising therapeutic strategies. The term "gene therapy" encompasses a diverse array of treatment modalities, all of which leverage genetic materials to alter cellular composition, either in a laboratory setting or within the living organism, with the ultimate goal of curing diseases [7]. A vast assortment of gene therapeutic agents has been subjected to rigorous testing across numerous in vitro and preclinical animal models, demonstrating remarkable efficacy. For instance, within models of lung cancer, gene therapy has been utilized to fabricate cancer vaccines, to direct viral agents towards cancerous cells to induce their self-destruction, to diminish the blood flow that nourishes tumors, and to insert genes into cancerous cells that either trigger cell death or incite a reversion to a normal cellular state, thereby enhancing survival rates. Preclinical assessments of gene therapy have similarly been extended to glioma, pancreatic and liver cancers, among numerous other malignancies. As with any innovative therapeutic approach, gene therapy is not without its profound safety considerations [7]. The initial fervor for gene therapy was somewhat quelled in 1999 following the tragic death of a subject involved in an escalating dosage gene therapy trial.

An additional emergent sphere within cancer gene therapy is the application of oncolytic vectors for the annihilation of cancer cells. Similar to immunotherapy, the foundational concept has been in existence for nearly a century, and, akin to immunotherapy, it is currently experiencing a renaissance through advancements in gene therapy. Oncolytic gene therapy vectors are predominantly viruses that have undergone genetic modification to specifically hone in on and eradicate cancerous cells, all the while sparing the remainder of the body's tissues. These vectors are engineered to penetrate cancerous cells and provoke cell death through the mechanisms of viral proliferation, expression of cytotoxic proteins, and cellular lysis. Preliminary trials of oncolytic therapy have underscored both its formidable potency and the distinctive hurdles inherent in its practical application. The outcomes of oncolytic gene therapy in mammalian models have been exceptionally promising. Within murine models, both colon and bladder cancers have exhibited improved survival rates and attenuated metastatic activity with the application of oncolytic viral agents [7]. However, oncolytic virus therapy confronts several unique impediments in human subjects. The majority of individuals possess antibodies against common viruses employed in treatment development, which frequently results in an immune response that neutralizes the virus before it can effectively infect the cells. Moreover, the utilization of viral particles capable of replication often necessitates heightened safety measures, thereby rendering clinical trials more costly and complex.

Given that oncolytic virus therapy is still in its relative infancy, there exists substantial potential for the refinement of therapeutic vectors. For viral therapy to achieve success, the production rate of viral particles within infected cancer cells must surpass the proliferation rate of the uninfected malignant cells. In the case of large, established tumors, accomplishing this can be challenging, suggesting that viral therapies may need to be integrated with conventional treatments, such as surgery, to initially deplete the cancer cell population. Furthermore, the most efficacious treatment protocols have yet to

be conclusively determined. In the initial study, the viral load necessary for systemic injections was found to be 1,000 times greater than that required for intertumoral injections [7].

Nonetheless, once these challenges are surmounted, oncolytic therapy presents a multitude of advantages. The selective nature of the viral therapy ensures minimal impact on healthy tissues. Furthermore, when combined with the expression of cytotoxic genes, this therapy affects not only rapidly dividing cells but also cells within the surrounding tissue, thereby creating an environment that is inhospitable to cancerous growth. The formidable lethality of these vectors, coupled with their selectivity, positions them as an exciting prospect in the reduction of cancer-related fatalities.

## Reference

- [1] Genetic mutations | Types of mutations. American Cancer Society. <https://www.cancer.org/cancer/understanding-cancer/genes-and-cancer/gene-changes.html>.
- [2] How cancer arises on JSTOR. [www.jstor.org](http://www.jstor.org).
- [3] GeneTherapy - Mayo Clinic. <https://www.mayoclinic.org/zh-hans/tests-procedures/gene-therapy/about/pac-20384619>.
- [4] What is Gene Therapy, <https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/what-gene-therapy>.
- [5] Du Cancer, C. C. S. / S. C. Genetic changes and cancer risk. Canadian Cancer Society. <https://cancer.ca/en/cancer-information/what-is-cancer/genes-and-cancer/genetic-changes-and-cancer-risk>.
- [6] Gülay Büyükköroğlu PhD, Duygu Abbasoğlu MSc & Candan Hızıl PhD “Breast Cancer Gene Therapy” (2014,p519-534), <http://www.nature.zd.hggfdd.top/articles/s41434-022-00379-6>.
- [7] Dastjerd, N. T., Valibeik, A., Rahimi Monfared, S., Goodarzi, G., Moradi Sarabi, M., Hajabdollahi, F., Maniati, M., Amri, J., & Samavarchi Tehrani, S. (2022). Gene therapy: A promising approach for breast cancer treatment. *Cell biochemistry and function*, 40(1), 28–48. <https://doi.org/10.1002/cbf.3676>.
- [8] What is gene therapy?: MedlinePlus Genetics. <https://medlineplus.gov/genetics/understanding/therapy/genetherapy/>.
- [9] Büyükköroğlu, G.; Abbasoğlu, D.; Hızıl, C. Breast cancer gene therapy. In Springer eBooks; 2014; pp 519–534. [https://doi.org/10.1007/978-81-322-0843-3\\_26](https://doi.org/10.1007/978-81-322-0843-3_26).