

## A NOVEL APPROACH IN THE TREATMENT OF ORAL CANCER- GENE THERAPY AN UPDATE

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### ABSTRACT

Gene therapy “the use of genes as medicine” involves the transfer of a therapeutic or working copy of a gene into specific cells of an individual in order to repair a faulty gene copy. Many experiments have been done with respect to its application in various diseases. Today, most of the gene therapy studies are aimed at cancer and hereditary diseases which are linked to genetic defects. The delivery system includes a vector that delivers a therapeutic gene into the patient’s target cell. Functional proteins are created from the therapeutic gene causing the cell to return to a normal stage. The vectors used in gene therapy can be viral and non-viral. Gene therapy, an emerging field of biomedicine, is still at infancy and much research

remains to be done before this approach to the treatment of condition will realize its full potential.

**KEYWORDS:** Gene therapy, Gene, Mutations, Cancer.

## INTRODUCTION

In this modern world Cancer is one of the fatal diseases amongst all the dreadful diseases. Cancer cells are different from other neighboring cells in having phenotypic changes in the manner of a rapid division rate Oral Squamous Cell Carcinoma is one of the commonly seen malignant lesions in the oral cavity, which is seen globally<sup>[1]</sup> and it is about the 6th most common cancer world-wide.<sup>[2]</sup> Oral cancer is associated with genetic mutations which occur due to the exposure to tobacco, alcohol, betel quid, etc.<sup>[3]</sup> It occurs in people who are aged 50 years or over. However, about 6% of the cases occur in young people who are under the age of 45 years.<sup>[4]</sup>

The introduction of new genes and the activation or inactivation of others may inhibit or suppress tumour growth. Gene therapy can potentially attack cancerous cells while respecting normal tissue. It may be useful to manage disease recurrence and as a coadjuvant therapy, e.g., in resected tumour margins. Clinical application of this technique in the treatment of oral cancer and precancer requires optimization of viral vectors and improvement of transfection effectiveness.

The aim of this review is to analyze the different modalities of gene therapy currently used to manage precancerous and cancerous lesions of the oral cavity.

### **The history of gene therapy**

Gene amplification, which is used in the treatment of various human diseases, was put forward by Cusack and Tanabe in 1998. Gene therapy is defined as gene transfer for the purpose of treating human diseases effectively (Cusack and Tanabe, 1998), which includes both the transfer of new genetic material and manipulation of the existing genetic material.<sup>[5]</sup> The first successful treatment was of X-linked Severe Combined Immunodeficiency (X-SCID) by *ex vivo* gene replacement therapy.<sup>[6]</sup>

### **Concept of gene therapy**

The objective of gene therapy is to introduce new genetic material into target (cancerous) cells while causing no damage to surrounding healthy cells and tissue. It has been defined as the “genetic modification of cells of a patient in order to fight a disease.”<sup>[7]</sup> Gene therapy includes both the transfer of new genetic material and the manipulation of existing genetic material. At the present time, the most widely used gene therapy procedure follows these steps:

- A. Identification, isolation and amplification of the gene to be used in the treatment.
- B. Extraction and in vitro culture of tissue cells from the patient to be treated.
- C. Transfer of the therapeutic gene into these cells via a vector, using a gene that contains a promoting sequence to enable its expression and a marker to identify cells into which it is incorporated
- D. Transfer into the patient of selected gene-containing cells. The theory is that when the gene exerts its normal physiological functions, the disease will be eliminated.

### **The Types of Gene Therapies<sup>[8]</sup>**

1. Germ line gene therapy
2. Somatic gene therapy

#### **1. Germ line gene therapy**

A mode of treatment where genes are incorporated into the reproductive cell/ tissues of the organism. In this technique, functional healthy genes are delivered to the egg/sperm cells. Two different types of treatment modalities have been advocated:

- a. Alteration/modification of genetic sequence of reproductive tissues before fertilization.
- b. Modification of genetic sequence at the blastomere stage. Germ line gene treatment is still in its infancy and a lot of research and clinical trials are underway, such as to make it a part of main stream medicine.

#### **2. Somatic gene therapy**

It is the alteration of genes in human somatic cells to treat a specific disorder.<sup>[1]</sup> Involves incorporation of functional genetic material into body cells and tissues other than the reproductive tissues. It is here, the risk of transfer of mutated genes to the next generation is considerably minimized. When compared to the germline gene therapy, this mode of treatment can be carried out easily. Numerous experimentation and clinical trials are being carried out in gene therapy, such that it can slowly but surely form a novel medical approach in successfully treating chronic ailments such as oral cancer, hemophilia and muscular dystrophy.

### **The Vectors in Gene Therapy**

Genetic material is delivered into the host cells through viruses or bacteria.<sup>[9]</sup> Gene therapy is concerned with DNA which can be delivered into cells by various methods. All viruses such as retroviruses, adenoviruses, lentiviruses, herpes simplex virus, vaccinia, pox virus and

adeno-associated virus bind to their hosts by introducing their genetic materials into the host cells. In gene therapy, the viral DNA can be removed, while the viruses can act as vehicles to deliver the therapeutic DNA into the host cells. The viruses which are used as vectors in gene therapy include retroviruses, adenoviruses, adenoassociated viruses and Herpes simplex virus.<sup>[1]</sup> The methods of non-viral gene therapy include the injection of naked DNA, electroporation, the gene gun and the use of oligonucleotides, dendrimers and inorganic nanoparticles. However, the non-viral vectors which are inhibited by the serum components, limit the efficiency of the gene delivery in vivo.<sup>[10]</sup> Despite the use of several nonviral methods, viruses provide a more efficient mode in gene therapy.<sup>[11]</sup>

### **The Technique of Gene Therapy**

The main objective of gene therapy is to introduce new genetic material into the target cells without causing any sort of damage to the surrounding normal cells. The therapies that express gene products, which result in the death of cancer cells, include, gene addition therapy, gene excision therapy, antisense RNA therapy, immunotherapy, suicide gene therapy, gene therapy with the use of oncolytic viruses, the introduction of genes to inhibit tumour angiogenesis and the delivery of drug resistance genes into normal tissues for protection against chemotherapy.<sup>[12]</sup> According to the results of animal studies which were done in mice, combination gene therapy which uses several genes, showed significant tumour regression in mice.<sup>[13]</sup>

### **Gene Addition Therapy**

Genetic alterations include mutations of p53, the Retinoblastoma Gene, p16 and p21. Among which, the tumour suppressor gene which is commonly used in gene therapy is the p53 gene<sup>[14]</sup> and about 60% of the human tumours are associated with mutations at the p53 locus.<sup>[15]</sup> In this technique, the tumour growth is controlled by the introduction of tumour suppressor genes which inactivate the carcinogenic cells.<sup>[12]</sup>

### **Gene Excision Therapy**

In this technique, the defective oncogenes are removed, as a result of which, there is an inhibition in the growth of the tumour cells.<sup>[12]</sup>

### **Antisense RNA Therapy**

The Antisense RNA checks the tumour growth by inhibiting the RNA which is complementary to the strands of the DNA which expresses that particular gene.<sup>[12]</sup>

### **Immunotherapy**

Oral cancer patients usually show defects or deficient immune cell functions of the natural killer cells, lymphocytes, cytokines, etc. This technique increases the immune response of the patients to the tumour.<sup>[12]</sup>

### **Suicide Gene Therapy**

Many studies have been done on the gene delivery system with retrovirus or adenovirus vectors.<sup>[16]</sup> This therapy involves enzymes, the expression of which transforms the non-toxic producing drug into an active cytotoxic substance.<sup>[12]</sup> It is the most commonly used gene therapy which uses thymidine kinase or other chemosensitizing genes.<sup>[17]</sup>

### **Gene Therapy with the Use of Oncolytic Viruses**

In this therapy, a vector (virus) is genetically modified, which replicates and lyses the tumour cells.<sup>[12]</sup> For example, adenovirus-mediated gene therapy is used for advanced cancers than traditional therapies.<sup>[18]</sup>

### **Advantages**

Despite of the disadvantages of gene therapy, it has advantages as well;

1. A functional gene has the ability to replace a defective gene.
2. Gene therapy aids in the prevention against the potentially toxic effects in the body, which can be caused by other therapies.
3. It decreases the cost of various therapies and improves the patient's life style for a longer period.<sup>[19]</sup>

### **Disadvantages of Gene Therapy**

1. Even after the therapeutic DNA is integrated into the genome, some cells prevent the gene therapy for long-term effects, for which patients may undergo multiple rounds of the gene therapy.
2. There is a possibility that the host's immune system and its response may reduce the effectiveness of the gene therapy.
3. The viral vectors can present a variety of potential problems to the patient, such as toxicity and immune and inflammatory responses.
4. Single gene disorders are the best candidates for gene therapy. But, some of the most commonly occurring diseases, such as heart disease, high blood pressure, Alzheimer's

disease, arthritis, and diabetes are multi-gene or multi-factorial disorders which are difficult to treat effectively with the use of gene therapy.

5. If the DNA is introduced into a wrong place in the genome, for example, into a tumour suppressor gene, it can induce a tumour.

## CONCLUSION

Gene therapy is an emerging field of biomedicine, with a potential to form a definitive treatment for oral cancer and other chronic ailments by offering greater effectiveness and possibly reducing the mortality rate. However, in the future the combination of gene therapy with chemotherapy and immunotherapy may form one of the most promising fields of research in the management of human diseases.

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