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Review Article

Gene Therapy in the Management of Head and Neck Cancers: A Review

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ABSTRACT

Cancer a general name for a group of more than 100 diseases is characterised by excessive and uncoordinated growth that persists in the same excessive manner after cessation of the stimuli which evoked the change. With a remarkable worldwide incidence oral squamous cell carcinoma commonly referred as oral cancer is one among the group that has a fairly poor prognosis. Despite advances in surgery, radiotherapy, and chemotherapy, the survival of patients with oral squamous cell carcinoma has not significantly improved over the past several decades. A novel approach to treatment that is currently being investigated is GENE THERAPY. Gene therapy essentially consists of introducing specific genetic material into target cells without producing toxic effects on surrounding tissue. Different treatment approaches are revealed for cancer gene therapy; gene addition therapy, suicide gene therapy, immunotherapy. In this paper different types of gene therapies are discussed along with an insight into future of this treatment modality.

Keywords: oral cancer, gene therapy, suicide gene therapy, immunotherapy.

INTRODUCTION

Head and neck cancers constitute the sixth most common malignancy [1] affecting mankind globally. Among them the vast majority (>90%) are squamous cell carcinomas. Oral cancer (OSCC, Oral Squamous Cell Carcinoma) is a genetic disease in which the genes that control cell growth and apoptosis are mutated, allowing cells to acquire the ability to invade and metastasize. [2] More than 300,000 new cases worldwide are being diagnosed with oral squamous cell carcinoma annually. This aggressive epithelial malignancy is associated with severe morbidity and less than 50% long term survival despite advances in treatment with surgery, radiation, and chemotherapy. The poor prognosis of oral cancer has not improved significantly over the last 4 decades. [3] Local and/or regional recurrence develops in approximately one-third of the patients despite definite treatment. [4]

The failure to conventional therapy occurs because in case of extensively large tumors it may be difficult to clear the margins or some tumors are remarkably resistant to radiotherapy or chemotherapy. Unacceptable degree of toxicity and bystander damage to normal tissue occurs if we increase the dose of radiation or chemotherapeutic drug. Combinations of current treatment modalities have been moderately successful, but often these combination therapies cause unacceptable toxicity without increasing the survival rate of patients. The major drawback for this conventional treatment is a lack of specificity for the tumor cells and toxicity to the normal tissues. [5]

New therapies, such as gene therapy, are being explored, for head and neck

cancer. The goal of gene therapy is to introduce new genetic material into cancer cells that will selectively kill the cancer cells with no toxicity to the surrounding non-malignant cells. For head and neck cancer, this is an attractive treatment, since the tumors are readily accessible for direct injection of gene therapy drugs and the normal tissues that would be preserved are often crucial for function. [6]

CONCEPT AND DEFINITION 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". [4] 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: identification, isolation and amplification of the gene to be used in the treatment; extraction and in vitro culture of tissue cells from the patient to be treated;

(i) 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; and

(ii) 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

HISTORY OF GENE THERAPY

The first FDA approved gene therapy experiment in the United States occurred in 1990 for a patient with severe combined immunodeficiency disorder. [7] Since then, many clinical trials have been conducted for patients with cancer, using different approaches in gene therapy, with successful results reported in patients with chronic lymphocytic leukemia, acute lymphocytic leukemia, brain tumors as well as others. Several commercially approved medications for gene therapy were released, including ONYX-15 for refractory head and neck cancer, [8] human papilloma virus vaccine for the prevention of cancer cervix. [9]

GENE TRANSFER DELIVERY SYSTEM

Several methods have been developed to facilitate the entry of genetic materials (transgenes) into target cells, using various vectors.

Requirements for Vector

The ideal requirements for vectors are: [10-12]

It should be non-immunologic

Should be stable and easy to reproduce

Should have longevity of expression

Should have high efficiency

High specificity and low toxicity

It should be able to protect and deliver DNA across the cell membrane into the nucleus. It should be able to target gene delivery to specific cells

It should be easy to be produced in large amounts and be inexpensive

Currently no single vector type will meet all needs for all tissues, that is different vectors will be needed for different clinical applications

TYPES OF VECTOR FOR GENE THERAPY

Vectors can be classified as either viral or non-viral vectors

Viruses usually bind to target cells and introduce their genetic materials into the host cell as part of their replication process. As they enter target cells, they can carry a load of other genetic material called "transgenes". For non-viral vectors, different approaches have been utilized, using physical, chemical, as well as other modes of genetic transfer. Transferring genetic material directly into cells is referred to as "transfection", while moving them into cells carried by a viral or bacterial vector is termed "transduction". Non-viral approaches have the advantage of safety and easy modifiability, but have a lower transfection efficiency compared to viral vectors

Physical mediated gene transfer

DNA genetic material that is coated with nanoparticles from gold or other

minerals, and with their kinetic energy supplemented by compressed air or fluid (gene gun), or using ultrasound, can force the genetic material into the target cell, followed by the release of DNA into its nucleus. They are best suited for gene delivery into tissue or in case of gene vaccination. [13]

The electroporation gene therapy approach aims to achieve cellular membrane disruption with high-voltage electrical pulses, resulting in the formation of nanopores through which naked DNA, foreign genetic materials, and even chemotherapeutic agents can enter cells. [13,14] This approach is best suited for plasmid DNA-based gene transfer therapy with the advantage of effectiveness in a vast array of cell types, ease of its administration, lack of genome integration with the risk of malignancy, as well as the low potential for unwanted immunogenicity. [15] Electroporation is presently being tested in several clinical trials, especially on patients with malignant melanoma, prostate cancer, colorectal cancer, and leukemia. [15]

Chemical mediated gene transfer

Cationic liposomes are microscopic vesicles of synthetic phospholipids and cholesterol that can enter into cells by endocytosis, [16] with the capability of carrying a variety of molecules such as drugs, nucleotides, proteins, plasmids and large genes. [13] Their advantage is selectivity to endothelial cells, a relatively high rate of gene transfer efficiency, a broad application as carriers for many genes, and the lack of severe side effects. [17] When combined with small interfering RNA (siRNA), cationic liposomes may lead to the inhibition of tumor proliferation, inducement of apoptosis, and enhancement of radio sensitivity to tumor cells. [18]

Synthetic viruses have been developed to exploit the efficiency of viral vectors and the advantage of liposomes. [19] Once they enter the target cell, DNA is released from the endosome. This method has shown promising results in preclinical studies. [20-23] Transposons can also transport genetic material inside the cell as well as into the nucleus. [24]

BACTERIAL MEDIATED GENE TRANSFER

Some bacteria have the capability of specifically targeting tumor cells, leading to RNA interference (RNAi) and gene silencing with blockage of RNA functions, including cellular metabolism and protein synthesis. Examples include Escherichia coli, Salmonella typhimurium, Clostridium, and Listeria. [25] Bacterial vectors can deliver pro-drug-converting enzymes and cytotoxic agents into tumor cells, and can mediate the host immune response. They can be engineered to carry magnetic or fluorescent material to enhance the utility of diagnostic approaches in tumor localization, such as with magnetic resonance imaging (MRI), [26] and even in the development of cancer vaccines. [27] However, the outcome has been far less pronounced compared to other RNA interference silencing techniques. Overall, genetically engineered bacteria acting as vectors for RNA interference are relatively safe, effective, practical and cheaper to manufacture compared to viral vectors. They selectively colonize and grow within the tumor. They can also be administered orally, hence their use in the management of gastrointestinal disorders. [25]

VIRAL VECTORS

Commonly used viral vectors are Adenovirus; Adeno associated virus (AAV), Retro virus and Herpes simplex virus. Among these, adenovirus is commonly used, as it can be cultured easily and is of lower pathogenicity. [11] These viruses are attenuated to transfect genes, but they cannot replicate or cause infection Eliminating their ability to replicate through genetic manipulation of the wild type virus eliminates the pathogenecity of virus. [12] A variety of virus vectors that have been employed to deliver genes have their own advantages and disadvantages. Gene transfer mediated by viral vectors is referred to as transduction. [28]

Adenoviruses

They infect both dividing cells and non dividing cells. Adenoviruses do not integrate the foreign DNA into host cells; rather the foreign DNA exists independently in the nucleus. Adeno associated virus, the smallest of three vectors listed, can accommodate only about half as much as foreign DNA as the others. This vector can insert their genetic material at specific site of chromosome 19. [29] Disadvantage of these vectors lies in the activation of both the innate and adaptive parts of the recipient's immune system when applied in vivo. [30]

Retroviruses

Retroviruses infect only dividing cells. They permanently integrate the foreign DNA into the host cell chromosomes and thus lead to stable expression. However, the gene insertion is not controlled, and it occurs in such a way as to cause a mutation of the cell. Retroviral vectors require mitotic cell division for transduction. [31]

Herpes simplex viruses

Double stranded viruses that infect particular cell type i.e. neurons. [29,32]

Types of gene delivery

***In vivo*:** delivery of gene takes place in the body. During in vivo gene transfer, the foreign gene is injected into the patient by viral and non viral methods.

***Ex vivo*:** delivery takes place outside the body and the cells are placed back in to the body. Ex vivo gene transfer involves a foreign gene transduced into tissue cells cultivated in laboratory outside the body, and then resulting genetically modified cells are transplanted back into the patient

GENE THERAPY STRATEGIES

In treating head and neck tumors with gene therapy, it is necessary to select a strategy that is appropriate to the molecular biology of these cancers all the strategies use an in vivo approach, since the tumors are generally accessible to direct injection the injected genes are designed to cause tumor cell death by creating toxic substances, replacing genes that will induce apoptosis, or inserting genes that will induce an antitumor immune response.

1. Gene Addition Therapy

The aim of this approach is to regulate tumour growth by introducing tumour suppressor genes that inactivate carcinogenic cells. [2] Cancer cells generally demonstrate impaired cell cycle progression, largely due to mutations and over expression of cell cycle regulators. Several genetic alterations have been described in oral cancer, including mutations of p53, the retinoblastoma gene (RB 1), P16 and p21. [4]

Most common tumor suppressor gene used in addition gene therapy is p53 with adenovirus as vector. A phase III study is currently under way on adenovirus vector Ad5CMV-p53. This is applied by intramucosal injection followed two hours later by a mouthwash.

From the next day, it is administered as a mouthwash twice a day for 2-5 days. This treatment is repeated every 28 days and has shown a capacity to inhibit disease progression in precancerous lesions with no toxic effects. [33] other tumour suppressor genes introduced are, [2]

A. Retinoblastoma gene (Rb) that causes alteration of Rb protein using OAS403 as vector (Ryan;2004)
B. mda-7(melanoma differentiation associated gene -7)
C. Manganese superoxide dismutase gene (MnSoD)-it suppresses tumor malignity by reducing peroxide flow and therefore cell mitosis (Liu et al; 1997)

Mutations of gene p27 are highly related to the appearance of tongue cancer gene transfer of p27 was found to inhibit the cell cycle of tumor cells ,inducing apoptosis and triggering the suppression of tumor growth. [2]

2. Gene Excision Therapy

The aim of this therapy is to remove defective oncogenes, thereby inhibiting growth of tumor cells. Okadaic acid a highly toxic polyether that inhibits phosphorylation of type 1 and 2A proteins,reducing expression of Egr-1(related to cell

proliferation and division) is used thereby inhibiting tumor activity.genes that control cell growth and cell cycle progression, including those that encode for tissue factors TGF-β1, PDGF-A and PTEN, are regulated by the expression of Egr-1,making this a good therapeutic approach. [2]

3. *Antisense RNA Therapy*

Antisense RNA may prevent the activity of oncogenes, including myc, fos and ras; and it can also inhibit viruses, e.g., HSV-1, HPV (Human Papillomavirus) and HTLV-1 (Human T-lymphotropic virus. Antisense RNA can check tumor growth usually by inhibiting RNAthat is complementary to the strand of DNA expressing the gene. [2]

Preclinical studies using antisense sequences under the control of six small RNA promoters demonstrated a powerful anti-tumour effect with minimum toxicity. [34] A phase 1 trial is under way in patients with advanced oral cancer to evaluate the safety and biological effects of administering liposome-mediated intratumoral EGFR (Epidermal Growth Factor Receptor) by means of antisense gene therapy. Results have been positive, showing a low toxicity and high efficacy. [35]

Limitations

Conventional use of this technique is limited by the difficulty of introducing a sufficient quantity of antisense molecules to inhibit tumour growth RNA interference (RNAi) based gene therapy; Small interfering RNA (siRNA) is primarily involved in guiding the degradation of messenger RNA. This form of gene therapy consists of two approaches:

1. Plasmid or viral vector -mediated delivery of short hairpin RNA precursors and
2. Direct delivery of siRNAs or siRNA precursors to target cells. [36]

Self-complementary recombinant adeno-associated virus (sc AAV) efficiently delivered siRNA into multidrug-resistant human breast and oral cancer cells and suppressed multidrug resistance-1 (MDR-1) gene expression. This resulted in rapid, profound, and durable reduction in the expression of the P-glycoprotein multidrug transporter, and a substantial reversion of the drug resistant phenotype. [37]

4. *Suicide Gene Therapy*

Suicide gene therapy for cancer inserts a gene into the tumor that encodes for a protein that will convert a nontoxic prodrug into a toxic substance. Also known as genetic prodrug activation therapy**.**

Herpes simplex virus thymidine kinase (HSV-tk) gene therapy was the first suicide gene therapy to be described and mostly investigated. [38,39] For this approach the tumor cells are genetically modified with HSV-tk gene and are then treated with the prodrug ganciclovir .HSV-tk enzyme phosphorylates ganciclovir to a monophosphate that is then further acted on by normal cellular enzymes to create ganciclovir triphosphate ganciclovir triphosphate inhibits DNA polymerase and is incorporated into DNA, causing chain termination and cell death. [40,41] unlike the prodrug ganciclovir ,its triphosphate form is unable to cross the cellular membrane and is trapped in the tumor cells.

Another form of suicide gene therapy uses the cytosine deaminase gene .the prodrug for this system is the minimally toxic 5 - fluorocytosine, which is converted in the tumor by cytosine deaminase into highly toxic 5-fluorouracil.

A phenomenon known as “Bystander Effect” is observed where cells neighboring those expressing HSVtk are also killed, [42] thereby, enhancing tumor cell kill. [43] Besides this, the HSVtk strategy is reported to enhance the NK cell killer activity in vivo by inducing the systemic immune response. [44]

5. *Gene Therapy Using Oncolytic Viruses*

A promising approach to gene therapy that involves use of viruses replicating in only tumor cells (oncolytic virus). The virus must be genetically modified to attenuate its toxicity in normal tissue while maintaining its oncolytic

activity against malignant tumours, with the aim of reinforcing safety without compromising the anti-tumour efficacyof the virus. [45] Replication of ONYX-015 adenovirus is minimal in cells with normal p53 function but reaches high levels in cells with p53 alterations or mutations. Intravenous injection of this vector produces important tumour regression and improves survival in presence of metastasis.

Patients with precancerous lesions were treated with Advexin® mouthwash (Introgen Therapeutics, Inc (INGN), NY), which also administers p53 by means of an adenovirus. Tissue analyses before and after treatment showed a marked decrease in the number and aggressiveness of precancerous cells. This treatment, currently in a phase II trial, also appears to be very well tolerated. [46] Intravenous injection of oncolytic adenovirus OAS403 showed cytotoxicity in tumor cells especially where Rb protein and the regulation of telomerase expression is altered. [47]

6. *Introduction Of Genes To Inhibit Tumor Angiogenesis*

One of the prerequisite conditions for the development of solid tumors is angiogenesis.tumor progression usually results from invasion of newly formed blood vessels by tumor cells. vaccines against receptor 2 of the VEGF factor (Vascular Endothelial Growth Factor), also known as FLK-1,is being developed that results in inhibition of angiogenesis, tumour growth and metastasis. The vaccine against FLK-1 is quite effective, stimulating T lymphocytes that inactivate this receptor. The vaccine will be useful in the treatment of tongue metastasis of OSCC, with an increased immune response. [48]

7. *Immunotherapy*

The aim of immunotherapy is to increase the patient's immune response to the tumour. Patients with OSCC present altered function of immune cells, including NK cells, T lymphocytes and numerous cytokines. Form animal studies it has been shown that IL-2 administration activates T lymphocytes and NK cells and that these in turn activate tumour necrosis factor α(TNF-α), triggered by the strong tumour inhibition effect. [4] Transduction of IL-2 gene, which appears to have an anti-tumour effect, by using the mutated fibroblast of an adenovirus and an RGD peptide (Adv-F/RGD), has been addressed. [49] The intratumoral injection of Adv-F/RGD showed a high anti-tumour effect due to increased mononuclear cell infiltration and major necrotic changes. Another therapeutic approach may be to use the monoclonal antibody Anti-ICAM-2 alongside the intratumoural gene transfer of interleukin-12

ICAM-2 is a glycosylated protein with surface adhesion that is expressed in endothelial cells and activates lymphocytes. Recent studies found that systemic administration of Anti-ICAM-2 induced the complete regression of OSCC lesions. However, the tumour regression is dependent on the immune system function and the induction of specific tumour toxins by the action of CD8 lymphocytes. [50]

Gene transfer of IL-12 using plasmid pNGVL3mIL12 is also being investigated. An FDA-approved clinical trial is under way but it is too early to predict results. [51]

Successful gene therapy requires that: [10]

Genetic nature of the disease is completely understood

Genes can be delivered to the target cells of affected tissue/organ

Transfected gene should be active for intended duration

Harmful side effects if seen should be manageable

Difficulties in gene therapy include: [29]

Difficulty to deliver genes in some sites like lung cells

Genes might integrate at sites where it can affect the functioning of another gene

Vectors may be recognized as -foreign by immune system triggering immune response

Viral vector may cause toxicity, inflammatory response and might recover their ability to cause disease

Multigene disorders are difficult to treat by gene therapy

Gene therapy is expensive

The most frequently observed adverse reactions to gene therapy are severe inflammatory processes and coagulopathies, generally in relation to the viral vectors employed. [2]

CONCLUSION

Gene therapy for cancer has evolved relatively fast in the last two decades, and presently, few drugs are commercially available while others are still in clinical trials. Most reports on gene therapy have shown good safety profiles with transient tolerable toxicities. The lack of success in several clinical trials may partly be attributed to patient selection. Patients with advanced and therapy - resistant malignancies are presently enrolled in gene therapy trials. Perhaps, gene therapy may be much more successful in patients with earlier stages of malignancies, or in those who have a lower tumor burden. Alternatively, gene therapy may better be used after successful cancer therapy with maximum tumor load reduction, such as after radical surgery, following radiation therapy, or after successful chemotherapy.

The clinical application of gene therapy for treatment of oral cancer will require optimization of gene delivery phase 2 clinical studies by various investigators have showed promising results when gene therapy is combined with chemotherapy, radiotherapy or surgery.

In the future, the wide use of patient and tumor genomic analysis as well as the assessment of host humoral and cellular immunity, will facilitate a better selection of the most appropriate gene therapy per patient. Recent progress in developing safe and effective vectors for gene transfer, such as with synthetic viruses and non-viral methods will increase the effectiveness and safety profile of gene therapy. Furthermore, with the advancement in biological research, much cheaper gene vectors will become commercially available, which will make gene therapy readily available to the majority of cancer patients, worldwide.

This will transform the future of cancer therapy, from generalized cancer treatment strategies, based on tumor size, nature and location, to a more tailored, individualized cancer therapy, based on the patient's specific genomic constituents, host immune status, and genetic profile of the underlying malignancy. Treatment is expected to be fast, effective, relatively less toxic and inexpensive, with higher cure rates.

REFERENCES

1. Hiraki A, Matsuo K, Wakai K, et al Gene-gene and gene-environment interactions between alcohol drinking habit and polymorphisms in alcohol-metabolizing enzyme genes and the risk of head and neck cancer in Japan. Cancer Sci 2007; 98:1087-91.
2. Ayllón-Barbellido S, Campo-Trapero J, Cano-Sánchez J, et al Gene therapy in the management of oral cancer: Review of the literature. Med Oral Patol Oral Cir Bucal. 2008; 13:15-21.
3. Greenlee RT, Murray T, Bolden S, et al. Cancer statistics, 2000. CA Cancer J Clin 2000; 50:7-33.
4. Xi S, Grandis JR. Gene therapy for the treatment of oral squamous cell carcinoma. J Dent Res. 2003; 82:11–6.
5. Moon C, Oh Y, Roth JA. Current status of gene therapy for lung cancer and head and neck cancer. Clin Cancer Res. 2003; 9:5055-67.
6. Gleich LL. Gene therapy for head and neck cancer. Laryngoscope. 2000; 110:708-26.
7. Sheridan C. Gene therapy finds its niche. Nat Biotechnol.2011; 29:121-128.
8. Chiocca EA, Abbed KM, Tatter S, et al. A phase I open-label, dose-escalation, multi-institutional trial of injection with an E1B-Attenuated adenovirus, ONYX-015, into the peritumoral region of recurrent malignant gliomas, in the adjuvant setting. Mol Ther.2004; 10(5):958-966.
9. Block SL, Nolan T, Sattler C, et al Protocol 016 Study Group Comparison of the immunogenicity and reactogenicity of a prophylactic quadrivalent human papillomavirus

(types 6, 11, 16, and 18) L1 virus-like particle vaccine in male and female adolescents and young adult women. Pediatrics.2006; 118(5):2135-2145.
10. Singh Arun, Badni Manjunath, Singh Anil, et al. Gene therapy for oral cancer - journey to a new horizon. Oral Maxillofacial Pathol J. 2012; 3:203-10.
11. Sunil Paramel Mohan, CR Ramachandran, N Jaisanghar, et al. Dental Surgeons as Gene Therapist. Intl J Oral Maxillofacial Pathol. 2012; 3:65-7.
12. Prabhakar AR, Paul M Jibi, Basappa N. Gene Therapy and its implications in Dentistry. Int J Clin Pediatr Dent. 2011; 4:85-92.
13. Baranyi L, Slepushkin V, Dropulic B. Ex vivo gene therapy: utilization of genetic vectors for the generation of genetically modified cell products for therapy. In: Lattime EC, Gerson SL, editors. Gene Therapy of Cancer. 3. San Diego (CA): Elsevier; 2013. pp. 3-18.
14. Yuan Z, Pastoriza J, Quinn T, et al. Targeting tumor vasculature using adeno-associated virus page vector coding tumor necrosis factor-a. In: Lattime EC, Gerson SL, editors. Gene Therapy of Cancer. 3. San Diego (CA): Elsevier; 2013. pp. 19-33.
15. Shirley S, Heller R, Heller L. Electroporation gene therapy. In: Lattime EC, Gerson SL, editors. Gene Therapy of Cancer. 3. San Diego (CA): Elsevier; 2013. pp. 93-106
16. Zabner J, Fasbender AJ, Moninger T, et al. Cellular and molecular barriers to gene transfer by a cationic lipid. J Biol Chem. 1995; 270(32):18997-19007.
17. Tagami T, Suzuki T, Matsunaga M, et al Anti-angiogenic therapy via cationic liposome-mediated systemic siRNA delivery.Int J Pharm. 2012;422(1-2):280-289.
18. Yang W, Sun T, Cao J, et al. Surviving down regulation by siRNA/cationic liposome complex radiosensitises human hepatoma cells in vitro and in vivo. Int J Radiat Biol. 2010; 86(6):445-457.
19. Wagner E, Plank C, Zatloukal K, et al. Influenza virus hemagglutinin HA-2 N-terminal fusogenic peptides augment gene transfer by transferrin-polylysine-DNA complexes: toward a synthetic virus-like gene-transfer vehicle. Proc Natl Acad Sci U S A.1992; 89(17):7934-7938.
20. Soltani F, Sankian M, Hatefi A, et al: Development of a novelhist one H1-based recombinant fusion peptide for targeted non-viral gene delivery. Int J Pharm 2013, 441(1–2):307-315.
21. Di Martino MT, Leone E, Amodio N, et al: Synthetic miR-34a mimics as a novel therapeutic agent for multiple myeloma: in vitro and in vivo evidence.Clin Cancer Res2012, 18(22):6260-6270.
22. Soliman M, Nasanit R, Abulateefeh SR, et al: Multicomponent synthetic polymers with viral-mimetic chemistry for nucleic acid delivery. Mol Pharm2012,9(1):1-13
23. Nie Y, Schaffert D, Rodl W , et al. Dual-targeted polyplexes: one step towards a synthetic virus for cancer gene therapy. J Control Release.2011; 152(1):127-134.
24. Hackett PB, Largaespada DA, Switzer KC, et al: Evaluating risks of insertional mutagenesis by DNA transposons in gene therapy.TranslRes2013, 161(4):265–283.
25. Kwon S, Min J: Genetically engineered Salmonella typhimurium for targeted cancer therapy. In Gene Therapy of Cancer.3rd edition. Edited by Lattime EC, Gerson SL. San Diego (CA): Elsevier; 2013:443-452.
26. Benoit MR, Mayer D, Barak Y , et al. Visualizing implanted tumors in mice with magnetic resonance imaging using magnetotactic bacteria. Clin Cancer Res. 2009; 15(16):5170-5177.
27. Baban CK, Cronin M, O'Hanlon D, et al. Improvements in gene therapy: averting the immune response to adenoviral vectors. Bio Drugs. 2002; 16(1):3-10Tangney M. Bacteria as vectors for gene therapy of cancer.Bioeng Bugs. 2010; 1(6):385-394.
28. Cotrim P Ana, Baum J Bruce. Gene Therapy: Some History, Applications, Problems, and Prospects. Toxicol Pathol. 2008; 36:97-103.
29. Chatterjee Anirban, Saluja Mini, Singh Nidhi. Gene therapy in periodontics. J

Indian Soc Periodontol. 2013; 17(2):156-161.
30. T Ritter, M Lehmann, H D Volk. Improvements in gene therapy: averting the immune response to adenoviral vectors. Bio Drugs. 2002; 16(1):3-10.
31. Robbins D Paul, Ghivizzani C Steven. Viral vectors for gene therapy. Pharmacol Ther. 1998; 80(1):35-47.
32. M Ali, NR Lemoine, C J Ring. The use of DNA viruses as vectors for gene therapy. Gene Ther. 1994; 1(6):367-84.
33. Liu TJ, Zhang WW, Taylor DL , et al. Growth suppression of human head and neck cancer cells by the introduction of a wild-type p53 gene via a recombinant adenovirus. Cancer Res. 1994; 54(14):3662-7.
34. 34. Bertrand JR, Pottier M, Vekris A , et al. Comparison of antisense oligonucleotides and siRNAs in cell culture and in vivo. Biochem Biophys Res Commun. 2002; 296(4):1000-4.
35. Waters JS, Webb A, Cunningham D, et al. Phase I clinical and pharmacokinetic study of bcl-2 antisense oligonucleotide therapy in patients with non-Hodgkin's lymphoma. J Clin Oncol. 2000; 18(9):1812-23.
36. Zhang C, Wang QT, Liu H, et al . Advancement and prospects of tumor gene therapy. Chin J Cancer 2011; 30:182-8.
37. Xu D, McCarty D, Fernandes A, et al . Delivery of MDR1 small interfering RNA by self complementary recombinant adeno-associated virus vector. Mol Ther 2005; 11:523-30.
38. Moolten FL. Tumor chemo sensitivity conferred by inserted herpes thymidine kinase genes: paradigm for a prospective cancer control strategy. Cancer Res 1986; 46:5276-5281.
39. Moolten FL, Wells JM. Curability of tumors bearing herpes thymidine kinase genes transferred by retroviral vectors. J Natl Cancer Inst 1990; 82:297-300 .
40. Reid R,Mar EC, Huang ES ,et al.Insertion and extension of acyclic, dideoxy,and ara nucleotides by herpes viridae, human alpha and human beta polymerase: a unique inhibition mechanism for 9-(1,2-dihydroxy-2-propoxymethyl)guanine triphosphate. J Biol Chem 1988; 263:3898-3904.
41. Mar EC , Chiou JF, Cheng YC, et al. Inhibition of cellular DNA polymerase alpha and human cytomegalovirus induced DNA polymerase by the triphosphate of 9-(2-hydroxyethoxymethyl) guanine and 9-(1, 2 - dihydroxy - 2 - propoxymethyl) guanine. J Virol 1985; 53:776-780.
42. Thomas SM, Naresh KN, Wagle AS,et al . Preclinical studies on suicide gene therapy for head/neck cancer: A novel method for evaluation of treatment efficacy. Anticancer Res 1998; 18:4393 -8.
43. Mullen CA, Anderson L, Woods K, et al. Ganciclovir chemoablation of herpesthymidine kinase suicide gene-modified tumors produces tumor necrosis and induces systemic immune responses. Hum Gene Ther 1998; 9:2019-30.
44. Hall SJ, Sanford MA, Atkinson G,et al . Induction of potent antitumor natural killer cell activity by herpes simplex virus thymidine kinase and ganciclovir therapy in an orthotopic mouse model of prostate cancer. Cancer Res 1998; 58:3221-5.
45. Wong RJ, Joe JK, Kim SH, et al. Oncolytic herpesvirus effectively treats murine squamous cell carcinoma and spreads by natural lymphatics to treat sites of lymphatic metastases. Hum Gene Ther. 2002; 13(10):1213-23.
46. Nemunaitis J, Ganly I, Khuri F, et al. Selective replication and oncolysis in p53 mutant tumors with ONYX-015, an E1B-55kD gene-deleted adenovirus, in patients with advanced head and neck cancer: a phase II trial. Cancer Res. 2000; 60(22):6359-66.
47. Hawkins LK, Lemoine NR, Kirn D. Oncolytic biotherapy: a novel therapeutic plafform. Lancet Oncol. 2002; 3(1):17-26.
48. Niethammer AG, Xiang R, Becker JC, et al. A dna vaccine against VEGF receptor 2 prevents effective angiogenesis and inhibits tumor growth. Nat Med. 2002; 8(12):1369-75.
49. Shillitoe EJ. Papillomaviruses as targets for cancer gene therapy. Cancer Gene Ther. 2006; 13(5):445-50.

50. Perez OD, Kinoshita S, Hitoshi Y,et al . Activation of the PKB/AKT pathway by ICAM2. Immunity. 2002; 16(1):51-65.
51. Imboden M, Shi F, Pugh TD, et al. Safety of interleukin-12 gene therapy against cancer: a murine biodistribution and toxicity study. Hum Gene Ther. 2003; 14(11):1037-48.

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