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# A Systematic Review of Gene Therapy as Treatment of Oral Squamous Cell Carcinoma

*by* Marhamah 04

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| FILE           | OF_GENE_THERAPY_AS_TREATMENT_OF_ORAL_SQUAMOUS_CELL_CARCINOMA.PDF (229.34K) | WORD COUNT      | 4088  |
| TIME SUBMITTED | 23-AUG-2020 08:40PM (UTC+0700)                                             | CHARACTER COUNT | 22108 |
| SUBMISSION ID  | 1372877731                                                                 |                 |       |

## A Systematic Review of Gene Therapy as Treatment of Oral Squamous Cell Carcinoma

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Article History: Submitted: 05.04.2020

Revised: 11.05.2020

Accepted: 23.06.2020

### ABSTRACT

**Background:** Oral squamous cell carcinoma (OSCC) represents about 90% of all malignant neoplasms of the oral cavity. Oral cancer is the cause of death among children ages 1-14 years. Gene therapy provides modern medicine and had great potential as a recent therapeutic modality. Gene therapy can potentially attack cancerous cells while respecting normal tissue. It may be useful as treatment for recurrence disease such as oral squamous cell carcinoma.

**Objective:** To review materials about gene therapy as a treatment for oral squamous cell carcinoma.

**Methods:** Scientific evidence and clinical cases were drawn from the literature to support this review and information about the gene therapy treatment of oral squamous cell carcinoma was collected.

**Results:** Gene therapy is introducing new genetic material into target 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. Gene therapy includes both the transfer of new genetic material and the manipulation of existing genetic material.

**Conclusion:** Gene therapy has potential as a recent treatment in cases of oral squamous cell carcinoma (OSCC).

**Keywords:** Gene therapy, Oral squamous cell carcinoma (OSCC)

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DOI: 10.31838/srp.2020.6.81

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### INTRODUCTION

Oral squamous cell carcinoma represents about 90% of all malignant neoplasms of the oral cavity in human.<sup>1</sup> Oral cancer is the 6<sup>th</sup> most common malignancy worldwide. Patients passed away because of cancer of the oral cavity and as much one hundred and forty five thousand patients.<sup>2</sup> According to histological data, oral squamous cell carcinoma accounts for majority of all oral cancer in the world.<sup>1</sup> Oral squamous cell carcinoma is rare in pediatric patients which defined by the American Academy of Pediatrics as patients under age 21. Many clinicians believe that this disease is associated with poorer survival compared to adults.<sup>3</sup>

The most risk factors of oral squamous cell carcinoma (OSCC) are tobacco and alcohol abuse. According to the International Agency for Research on Cancer that cigarettes smoke contains more than 60 chemical carcinogens.<sup>2</sup> Alteration of taste, pain, difficulty in eating, bacterial and fungal infections, mucosal ulceration, increased thickness of saliva, discoloration skin, and edema of the skin are the side effects.<sup>3,4</sup>

Gene therapy provides modern medicine and had great potential as a recent therapeutic modality. Clinical application of this technique in the treatment of oral cancer and precancer requires optimization of viral vectors and improvement of transfection effectiveness.<sup>7,8,9</sup> Here we use systematic review and meta-analysis to describe more deeply

about gene therapy as a treatment of oral squamous cell carcinoma.

### Oral Squamous Cell Carcinoma (OSCC)

Oral cancer is the 6<sup>th</sup> most common malignancy worldwide. Patients passed away from cancer of the oral cavity and lip as much one hundred and forty five thousand.<sup>2,4</sup> The etiology of oral squamous cell carcinoma there are:

a. Tobacco

More than 80% consumption of tobacco with smoking greatly increases the risks of oral squamous cell carcinoma. The strongest being tobacco-specific N-nitrosamines is several carcinogens in tobacco.<sup>10,11,12</sup>

b. Alcohol

The combined use of alcohol and tobacco has a multiplicative effect on oral cancer risk. The various pathways by which alcohol may exert carcinogenic influence include topical exposure leading to a direct effect on cell membranes.<sup>10,13</sup>

c. Genetic

Cytochrome p450 system is most carcinogens which metabolized in the liver. Individuals with the fast metabolizing version of alcohol dehydrogenase have a greater risk of developing oral cancer.<sup>10,14,15</sup>

Potential symptoms of the oral squamous cell carcinoma:<sup>12</sup>

- Non healing ulcer with or without induration
- White patch with firm consistency

- c. Red lesion or with erythroplasia
- d. Abnormal lump in the mouth
- e. Exophytic proliferative growth
- f. Lymph node enlargement

The mechanism of pathogenesis of oral squamous cell carcinoma there is genetic alterations include activation of oncogenes that promote proliferation as well as inactivation of TSGs. In oral dysplastic lesions and oral squamous cell carcinoma, the increased expression of antiapoptotic proteins either Bcl-2 has been detected.<sup>16,17,18,19,20</sup>

Managements for oral squamous cell carcinoma<sup>21,22,23,24,25</sup>

#### a. Chemoradiotherapy

The first line of treatment of oral squamous cell carcinoma is chemotherapy using drugs like cisplatin, 5-fluorouracil, and docetaxel. Chemotherapy is effective in oral carcinoma when used in combination.

#### b. Surgical Interventions

Surgical removal of the tumor is done if the tumor is small enough and if surgery is likely to result in functionally satisfactory results. When a tumor is inoperable, chemoradiotherapy is often used with surgery. After the surgery, most oral cancer patients, depend on a feeding tube for their nutrition.

#### c. COX-2 Inhibitors

Cyclooxygenases (COX) are rate limiting enzymes as catalysts in the synthesis of prostaglandins from arachidonic acid. COX-2 is an inducible enzyme that is elevated during inflammation.

#### d. Photodynamic Therapy

Several small clinical studies have shown that photodynamic therapy is effective in treating premalignant lesions and superficial carcinoma. Hematoporphyrin derivatives and its conjugates are administered either topically or by intravenous route.

#### e. Gene Therapy

Gene therapy is a gene transfer for treating human diseases, which includes both manipulation of the existing genetic material and the transfer of new genetic material. The first successful treatment was of X-linked Severe Combined Immunodeficiency (X-SCID) by ex vivo gene replacement therapy.<sup>7,26</sup>

The purpose of gene therapy is introducing new genetic material cancerous cells while causing no damage to surrounding healthy cells and tissue. At the present time, the most widely used gene therapy procedure follows these steps:<sup>7,27,28</sup>

- 1) Identification, isolation and amplification of the gene to be used in the treatment for patients.
- 2) Extraction and in vitro culture of tissue cells from the patient to be treated.
- 3) 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.

- 4) Transfer into the patient of selected gene containing cells. The theory is that when the gene exerts its normal physiological functions.

The main purpose of gene therapy is to introduce new genetic material into the target cells without causing of damage to the surrounding normal cells. The technique of gene therapies are:<sup>28,29,30,31</sup>

#### A. 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.

#### B. Gene Addition Therapy

Genetic alterations include mutations of p53, the retinoblastoma gene, p21, and p16. Tumour suppressor gene which is commonly used in gene therapy is the p53 gene and 60% of the human tumours are associated with mutations at the p53 locus.

#### C. 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.

#### D. Suicide Gene Therapy

Many studies have been done on the gene delivery system with retrovirus or adenovirus vectors. This therapy involves enzymes, the expression of which transforms the non-toxic producing drug into an active cytotoxic substance.

Advantages of gene therapy are:<sup>9,12,33</sup>

1. Functional gene can replace a defective gene.
2. Aids in the prevention of potentially toxic effects in the body.
3. It decreases the cost of various therapies and improves the patient's lifestyle for a longer period.

## 13 METHODS

### Literature Search and Research Methods

Relevant full publications and meeting abstracts were identified by electronic searching of online databases (ClinicalTrials.gov, National Library of Medicine) using the search term: <gene therapy> AND <oral squamous cell carcinoma>.<sup>16</sup> The methods of this research are:<sup>17</sup>

### 6 Cell Culture

This study used the TCA8113 (tongue squamous cell carcinoma), MG63 (osteosarcoma), Eca-109 (esophageal cancer), HeLa (endocervical adenocarcinoma), MCF-7 (breast cancer) human cancer cell lines, and the L02 (spontaneously immortalized hepatic cells) normal cell line.

### 1 Real-Time Fluorescence Quantitative PCR

Total RNA was isolated from cells according to the instructions of a TaKaRa Mini BEST Universal RNA Extraction Kit. The amplification was monitored on an ABI Prism 7500 real-time PCR apparatus (Applied Biosystems) using SYBR Green detection chemistry (TaKaRa).

### 1 Cells Early Apoptotic Changes Detected by TUNEL Assay

The cells were cultured and transfected as described above. Afterward, the cells were collected after plasmid transfection and evaluated using a TUNEL cell apoptosis assay kit (Biyuntian Biotechnology Co., Ltd.).

### 6 Data Extraction and Analysis

Statistical analyses were performed using GraphPad Prism 5.0. All data were expressed as the mean SEM. Differences with P values <0.05 were considered significant.

## 1 RESULTS

### 1 Expression of the SERPINB3 Gene in Different Human

1 Cell Lines Determined by Western Blotting and RT-qPCR To determine the potential of the SERPINB3 gene for the targeted therapy of squamous cell carcinoma, we detected the expression of the SERPINB3 gene in different cell lines (TCA8113, HeLa, MG63, L02) by Western blotting and RT-qPCR.<sup>17</sup>

### 1 Inhibition of Protein Synthesis Induced by the SERPINB3-PE38KDEL Plasmid

1 These results showed that among the plasmids tested, the recombinant toxic gene expression plasmid pSERPINB3-PE38KDEL inhibited the expression of luciferase in TCA8113 cells most strongly, which indicated that the plasmid strongly inhibits protein synthesis in TCA8113 cells.<sup>17</sup> (Figure 1).

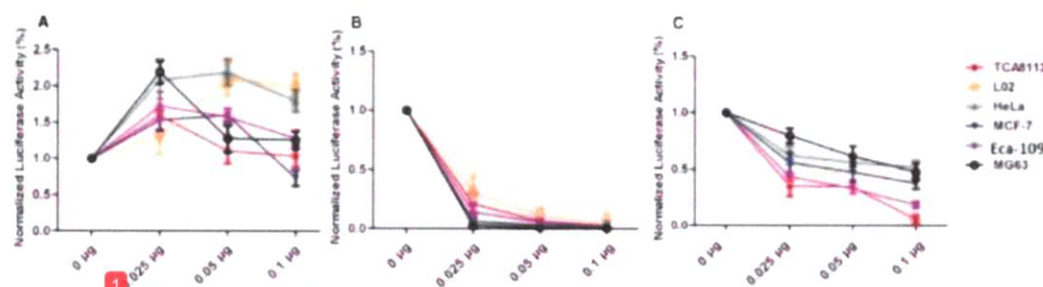


Figure 1: Inhibition of protein synthesis induced by the pSERPINB3-PE38KDEL plasmid. A) After 48 h of cotransfected with different quantities (0 µg, 0.025 µg, 0.05 µg, or 0.1 µg) of the negative control plasmid pGL3-Basic. B) After 48 h of transfected with different quantities (0 µg, 0.025 µg, 0.05 µg, or 0.1 µg) of the positive control plasmid pcDNA-PE38KDEL. C) After 48 h of cotransfected with different quantities of the pSERPINB3-PE38KDEL plasmid (0 µg, 0.025 µg, 0.05 µg, or 0.1 µg).

(Source: Wu J, Guo Q, Zhang G, et al. (2020). Study on the targeted therapy of oral squamous cell carcinoma with a plasmid expressing PE38KDEL toxin under control of the SERPINB3 promoter. *Cancer Med*. 00:1–10

### 6 Early Apoptosis Analysis by TUNEL Assay

These results showed that the rate of TCA8113 cell apoptotic necrosis was significantly higher than that of MG63 and L02 cells after 48 hours of transfection.<sup>17</sup>

## 3 DISCUSSION

Today, the research on gene therapy in oral cancer is increasing in the laboratory and the clinical settings. Gene therapy is now moving from phase 1 and 2 trials to the next level. Considerable time and a large number of patients are required to demonstrate the true efficacy of the therapies.<sup>7,24</sup> Combination gene therapy which uses several genes showed significant tumor regression in animal studies. The results showed a low toxicity and high efficacy.<sup>15,36,37,38</sup> In India, Advanced Centre for Treatment, Research and Education for Cancer (ACTREC, Mumbai) was the first centre dedicated to gene therapy research. Rita Mulherkar's group from ACTREC is conducting gene therapy studies related to the treatment of HNC using viral vectors.<sup>16</sup> The clinical application of gene therapy for treatment of oral cancer will require optimization of gene delivery.<sup>19,40,41,42</sup>

Phase II clinical studies by various investigators have showed promising results when gene therapy combined with chemotherapy, surgery, or radiation therapy. Such augmentative approaches, will reduce morbidity of the treatment and help maintain quality of life in patients with oral squamous cell carcinoma.<sup>13,41,45</sup>

As shown in this review, research on gene therapy in oral cancer is increasing in the laboratory and in the clinical settings. At present, the use of adenoviruses to act at altered gene level and the combination of this technique with chemotherapy or immunotherapy appear to be the most promising approaches to the management of oral cancer and precancer.<sup>6</sup>

In the 1970, Kato and Torigoe isolated squamous cell carcinoma specific antigen from cervical squamous cell carcinoma. The antigen is composed of two isomers with almost the same molecular weight, SERPINB3 and SERPINB1 among which SERPINB3 is a serine protease inhibitor. The Western blotting and RT-qPCR results in this study proved that the SERPINB3 gene was expressed.<sup>17,47</sup>

According to search conducted by U.S. National Library of Medicine, some cancers that occur in the mouth may in some way be due to a defect in a gene called the p53 gene. The parts of the adenovirus that allow it to reproduce and promote infection are removed, and the experimental gene (p53) is added.<sup>18</sup>

The mouth rinse will be given the time on the first day and two times on days 2 until 5. The injection and rinse (first day of each cycle), or the two rinses (days 2 and 4 of each cycle), will be separated by at least two hours. Eating and drinking should be avoided for one hour after receiving the mouth rinse. The injection and rinse series will be repeated on a monthly basis for a period of six months.<sup>18, 19</sup>

Participants will be requested to have two biopsies (small tissue samples) of the premalignant lesion taken on day 5 of the 4<sup>th</sup> and 6<sup>th</sup> courses. These studies will also determine if the gene therapy injections have been effective in delivering p53 gene (p53) to the precancerous cells.<sup>18</sup>

Gene transfer, while a radical new type of treatment, is also the only gene therapy product to obtain regulatory approval in any global market, as demonstrated by China's 2003 approval of Gendicine for clinical use. Gendicine is a modified adenovirus that delivers the p53 gene to cancer cells and is approved for the treatment of head and neck squamous cell carcinoma.<sup>20</sup>

Gene transfer technology allows an incredible diversity of treatment possibilities. New delivery methods and more sophisticated gene expression cassettes will create better therapeutic alternatives to make the goal of cancer treatment and eradication achievable.<sup>20, 21, 22, 23</sup>

## CONCLUSION

Gene therapy has potential as a treatment in cases of oral squamous cell carcinoma (OSCC).<sup>26</sup>

## REFERENCES

1. Chaudhary N, Gupta DK, Verma RK, Choudhary SR. (2016). Squamous cell carcinoma of tongue in a 12-year-old child. *Acta Oto-Laryngologica Case Reports*, 1(1), 87-89. DOI: 10.1080/23772484.2016.1239183.
2. Dhanuthai K, et al. (2018). Oral cancer: a multicenter study. *Med Oral Patol Oral Cir Bucal*. 1:23 (1):e23-9.
3. Muthu K, Vaishnavi V, Sivadas G. (2018). Warning signs and symptoms of oral cancer and its differential diagnosis. *J Young Pharm*. 10(2): 138-143.
4. Morris LG, Ganly I. (2010). Outcomes of oral cavity squamous cell carcinoma in pediatric patients. *Oral Oncol*. 46(4): 292-296.
5. Sidell D, Nabili V, Lai C, Cheung G, Kirsch C, Abemayor E. (2009). Pediatric squamous cell carcinoma: case report and literature review. *The American Laryngological, Rhinological and Otolaryngological Society, Inc*. 119:1538-1541. DOI: 10.1002/lary.20531.
6. Blanchard P., B. Baujat, V. Holostenco, A. Bourredjem, C. Baey, et al. (2011). Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC): A Comprehensive Analysis by Tumour Site. *Radiotherapy and Oncology*. 100 (1): 33-40.
7. Singh R, Singh S, Kumar T, Kumar A, Kumar A, Nazeer J. (2017). A novel approach in the treatment of oral cancer- gene therapy an update. *World Journal of Pharmacy and Pharmaceutical Sciences*. 6(4): 283-289.
8. Kumar A, Agrawal A, Sreedevi R. (2015). Novel therapy for oral cancer - gene therapy an update. *British Journal of Medicine & Medical Research*. 9(3): 1-8.
9. Jacob KC, Yashoda R, Puranik MP. (2015). Gene therapy in the treatment and prevention of oral cancer: an overview. *International Journal of Advanced Health Sciences*. 2(2): 14-20.
10. Radoi L, Bailly SP, Papadopoulos DCA, Guida F, et al. (2013). Tobacco Smoking, Alcohol Drinking and Risk of Oral Cavity Cancer by Subsite: Results of a French Population-Based Case-Control Study, the ICARE Study. *European Journal of Cancer Prevention*. 22 (3): 268-76.
11. Gandini SE, Boffetta NP, La VC, Boyle P. (2012). Mouthwash and oral cancer risk quantitative meta-analysis of epidemiologic studies. *Annals of Agricultural and Environmental Medicine*. 19 (2): 173-80.
12. Lu D, Yu X, Du Y. (2011). Meta-Analyses of the Effect of Cytochrome P450 2E1 Gene Polymorphism on the Risk of Head and Neck Cancer. *Molecular Biology Reports* 38 (4): 2409-16.
13. Johnson N, Warnakulasuriya WS, Gupta PC, Dimba E, Chindia M, et al. (2011). Global oral health inequalities in incidence and outcomes for oral cancer: causes and solutions. *Advances in Dental Research*. 23 (2): 237-46.
14. Chandra A, Sebastian BT, Agnihotri A. (2013). Oral squamous cell carcinoma pathogenesis and role of p53 protein. *Universal Research Journal of Dentistry*. 3(3): 128-130.
15. Gharat SA, Momin M, Bhavsar C. (2016). Oral squamous cell carcinoma: current treatment strategies and nanotechnology-based approaches for prevention and therapy. *Critical Reviews in Therapeutic Drug Carrier Systems*. 33(4): 363-400.
16. Hirst TC, Vesterinen HM, Conlin S, Egan KJ, Antonic A, McLean, Macleod MR, Grant R, Brennan PM, Sena ES, Whittle IR. (2015). A systematic review and meta-analysis of gene therapy in animal models of cerebral glioma: why did promise not translate to human therapy? *Evidence-based Preclinical Medicine*. 1(1): 21-33. DOI: 10.1002/ebm2.6.
17. Wu J, Guo Q, Zhang G, et al. (2020). Study on the targeted therapy of oral squamous cell carcinoma with a plasmid expressing PE38KDEL toxin under control of the SERPINB3 promoter. *Cancer Med*. 00:1-10. <https://doi.org/10.1002/cam4.2880>
18. Misra S. (2013). Human Gene Therapy : A Brief Overview of the Genetic Revolution. *Journal Association of Physicians India*. 61: 127-133.
19. Bugshan A and Farooq I. (2020). Oral squamous cell carcinoma: metastasis, potentially associated malignant disorders, etiology and recent

- advancements in diagnosis [version 1; peer review: 3 approved] *F1000Research*. 9:229.
20. Liu L, Chen J, Cai X, Yao Z, Huang J. (2019). Progress in targeted therapeutic drugs for oral squamous cell carcinoma. *Surg Oncol*. 31:90-97.
  21. Patil PM, Chaudhari PD, Sahu M, Durangkar NJ. (2012). Review article on gene therapy. *International Journal of Genetics*. 4(1): 74-79.
  22. O'Malley BW, Chen JSH, Schwartz MR, Woodruff STC. (1995). Adenovirus-mediated Gene Therapy for Human Head and Neck Squamous Cell Cancer in a Nude Mouse Model. *CANCER RESEARCH* 55. 1080-1005.
  23. Gonçalves GAR, Paiva RMA. (2017). Gene therapy: advances, challenges and perspectives. *Reviewing Basic Sciences*. 15(3):369-75.
  24. Nemunaitis J, Clayman G, Agarwala SS, Hrushesky W, Wells JR, Moore C et al. (2009). Biomarkers Predict p53 Gene Therapy Efficacy in Recurrent Squamous Cell Carcinoma of the Head and Neck. *Clin Cancer Res*. 15(24). 7719-7725.
  25. Kashif M, Ishfaq M, Nagil AH. (2015). Expression of Prostanoid EP3 Receptors in Oral Squamous Epithelium and Oral Squamous Cell Carcinoma. Hindawi Publishing Corporation. Pathology Research International. Article ID 602929. 7 pages. <http://dx.doi.org/10.1155/2015/602929>.
  26. Hunt KK, Vorburger SA, Swisher SG. (2008). Gene Therapy for Cancer. *British Journal of Cancer*. 98, 674 - 675.
  27. Schoop RAL, Noteborn MHM, Jong RJB. (2009). A mouse model for oral squamous cell carcinoma. *J Mol Hist* (2009) 40:177-181. DOI 10.1007/s10735-009-9228-z.
  28. Cotrim AP, Baum BJ. (2008). Gene Therapy: Some History, Applications, Problems, and Prospects. *Toxicologic Pathology*, 36:97-103.
  29. Shinohara ET, Lu B, Hallahan DE. (2004). The Use of Gene Therapy in Cancer Research and Treatment. *Technology in Cancer Research & Treatment*. 3(5): 479-490.
  30. Stoner N. (2009). Gene Therapy Applications. *Clinical Pharmacist*. p.270-273.
  31. Thakur C. (2016). Gene Therapy for Cancer Treatment. *Research & Reviews: Journal of Medical and Health Sciences*. 5(3): 1-5.
  32. Ginn SL, Alexander IE, Edelstein ML, Abedi MR, Wixon J. (2013). Gene therapy clinical trials worldwide to 2012 - an update. *J Gene Med*. 15: 65-77. DOI: 10.1002/jgm.2698.
  33. Ginn SL, Amaya AK, Alexander IE, Edelstein M, Abedi MR. (2018). Gene therapy clinical trials worldwide to 2017: An update. *J Gene Med*. 20:e3015. <https://doi.org/10.1002/jgm.3015>.
  34. Zhang et al. (2011). Gene therapy for oral squamous cell carcinoma with IA1.3B promoter-driven oncolytic adenovirus-infected carrier cells. *ONCOLOGY REPORTS* 25: 795-802.
  35. High KA, Roncarolo MG. (2019). *Frontiers in Medicine Gene Therapy*. n engl j med 381:5.
  36. Bayle et al. (2016). Molecular Classification of Oral Squamous Cell Carcinoma. *Journal of Clinical and Diagnostic Research*. 2016 Sep. Vol-10(9): ZE18-ZE21.
  37. Mueller et al. (2010). *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 109:694-699.
  38. Masaya Nishikawa et al. (2003). Cell death of human oral squamous cell carcinoma cell line induced by herpes simplex virus thymidine kinase gene and ganciclovir. *Nagoya J. Med. Sci*. 66. 129 - 137.
  39. Sayed-Ahmed MZ, Makeen HA, Elsherbini MM, Syed NK, Shoeb SM (2018) *Oncolytic Viruses: A gene Therapy for Treatment of Cancer in Companion Animals*. *Health Sci J Vol.12.No.4*:579.
  40. Ortiz et al. (2012). New Gene Therapy Strategies for Cancer Treatment: A Review of Recent Patents. *Recent Patents on Anti-Cancer Drug Discovery*. 7, 297-312.
  41. Rodrigues CR, Garcia LR, Baptista PV, Fernandes AR. (2020). Review Gene Therapy in Cancer Treatment: Why Go Nano? *Pharmaceutics*. 12, 233.
  42. Li et al. (2015). *Journal of Experimental & Clinical Cancer Research*. 34:97. DOI 10.1186/s13046-015-0211-0.
  43. Zarogoulidis et al. (2013). *J Genet Syndr Gene Ther*. 4:4. DOI: 10.4172/2157-7412.1000139.
  44. Turato C, Pontisso P. (2015). SERPINB3 (serpin peptidase inhibitor, clade B (ovalbumin), member 3). *Atlas Genet Cytogenet Oncol Haematol*. 19:202-209.
  45. Duarte S, Carle G, Faneca H, Lima MCPd, Pierrefite-Carle V. (2012). Suicide gene therapy in cancer: where do we stand now? *Cancer Lett*. 324(2):160-170.
  46. Emens LA. (2010). Chemo immunotherapy. *Cancer J*. 16(4):295-303.
  47. Huldani, Achmad H, Arsyad A, Putra AP, Sukmana BI, Adiputro DL, Kasab J. (2020). Differences in VO2 Max Based on Age, Gender, Hemoglobin Levels, and Leukocyte Counts in Hajj Prospective Pilgrims Regency, South Kalimantan. *Systematic Reviews in Pharmacy*. 11(4): 09-14.
  48. Xu J, Wang S, Ke B, et al. (2017). Research progress of gene therapy for cancer. *Chin Gen Pract*. 15:655-658.
  49. U.S. National Library of Medicine. (2010). Wild Type p53 Adenovirus for Oral Premalignancies. *ClinicalTrials.gov*. (<https://www.clinicaltrials.gov/ct2/show/NCT00410865?term=%22gene+therapy%22+OR+%22gene+transfer%22+OR+%22virus+delivery%22&cond=Cancer&draw=10&rank=87>)
  50. Riyanti E, Achmad H, Safari MH, Gartika M, Ramadhany YF. (2020). Analysis of VDR Gene Polymorphism in Beta Thalassemia Major (Beta Thalassemia Major / Vitamin D / Calcium / 825T/T Vitamin D Receptor Gene). *Systematic Reviews in Pharmacy*. 11(4): 268-274.
  51. Barbellido SA, Trapero JC, Sánchez JC, García MAP, Castaño NE, Martínez AB. (2008). Gene therapy in the management of oral cancer: Review of the literature. *Med Oral Patol Oral Cir Bucal*. 13(1):E15-21.
  52. Cross D, James K, Burmester. (2006). Gene Therapy for Cancer Treatment: Past, Present and Future. *Clin Med Res*. 4(3): 218-227.

53. Huldani, Pattelongi I, Massi MN, Idris I, Bukhari A, Widodo ADW, Achmad H. (2020). Research Reviews on Effect of Exercise on DAMP's, HMGB1, Proinflammatory Cytokines and Leukocytes. *Systematic Reviews in Pharmacy*. 11(4): 306-312.

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| <b>6</b> | Jiang Wu, Qiong Guo, Guoliang Zhang, Liying Zhao, Yv Guang Lv, Jiaqi Wang, Jiguang Liu, Wei Shi. "Study on the targeted therapy of oral squamous cell carcinoma with a plasmid expressing PE38KDEL toxin under control of the SERPINB3 promoter", Cancer Medicine, 2020<br>Publication | <b>%1</b> |

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| 8  | Sankalp A. Gharat, Munira Momin, Chintan Bhavsar. "Oral Squamous Cell Carcinoma: Current Treatment Strategies and Nanotechnology-Based Approaches for Prevention and Therapy", <i>Critical Reviews™ in Therapeutic Drug Carrier Systems</i> , 2016<br>Publication | %1 |
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| 13 | <a href="http://www.research.ed.ac.uk">www.research.ed.ac.uk</a><br>Internet Source                                                                                                                                                                               | %1 |
| 14 | Luc G.T. Morris, Ian Ganly. "Outcomes of oral cavity squamous cell carcinoma in pediatric patients", <i>Oral Oncology</i> , 2010<br>Publication                                                                                                                   | %1 |
| 15 | <a href="http://www.sciencedomain.org">www.sciencedomain.org</a><br>Internet Source                                                                                                                                                                               | %1 |

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| 17 | <a href="http://worldwidescience.org">worldwidescience.org</a><br>Internet Source                                                                                                                                                                                                        | % 1 |
| 18 | "Encyclopedia of Cancer", Springer Science and Business Media LLC, 2009<br>Publication                                                                                                                                                                                                   | % 1 |
| 19 | <a href="http://fr.scribd.com">fr.scribd.com</a><br>Internet Source                                                                                                                                                                                                                      | % 1 |
| 20 | Maria Noel Marzano Rodrigues Petruzzi, Karen Cherubini, Fernanda Gonçalves Salum, Maria Antonia Zancanaro de Figueiredo. "Role of tumour-associated macrophages in oral squamous cells carcinoma progression: an update on current knowledge", Diagnostic Pathology, 2017<br>Publication | % 1 |
| 21 | Submitted to Pacific University<br>Student Paper                                                                                                                                                                                                                                         | % 1 |
| 22 | Neena Chaudhary, Deepak K. Gupta, Rajeev Kumar Verma, Santosha R. Choudhary. "Squamous cell carcinoma of tongue in a 12-year-old child", Acta Oto-Laryngologica Case Reports, 2016<br>Publication                                                                                        | % 1 |
|    | <a href="http://jisikworld.com">jisikworld.com</a>                                                                                                                                                                                                                                       |     |

23

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[www.ompj.org](http://www.ompj.org)

Internet Source

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25

Aminuddin Prahatama Putra, Muslimin Ibrahim, Huldani Huldani, Bayu Indra Sukmana, Fauziah Fauziah, Harun Achmad. "Are There Levels of Students Morales? The Effects of Biological Problem Solving on Moral Development", International Education Studies, 2020

Publication

<% 1

26

"Contemporary Oral Oncology", Springer Science and Business Media LLC, 2017

Publication

<% 1

27

Chiang, W.F.. "Overexpression of galectin-1 at the tumor invasion front is associated with poor prognosis in early-stage oral squamous cell carcinoma", Oral Oncology, 200804

Publication

<% 1

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