International Journal of Biology and Life Sciences
ISSN: 2957-9511 | Vol. 10, No. 3, 2025

Gene Therapy Strategies and Applications for Cancer

Xinyan Lou

College of Laboratory Medicine (College of Life Sciences), Wenzhou Medical University, Wenzhou, Zhejiang, 325035, China

Abstract: With the advancement of medical technology, people have made some new progress and breakthroughs in the treatment of tumors and cancers, especially in the aspect of genetic intervention, This paper introduced the process of different gene therapy strategies for treating diseases and the application of various gene therapy strategies in tumor treatment research, which can provide researchers with a basic knowledge framework for gene therapy of cancer, and provide fundamental ideas for the study of cancer pathogenesis, pathogenic genes, etc.

Keywords: Gene Therapy; Tumor Treatment; Gene Expression.

1. Introduction

The gene intervention strategy for cancer is a biomedical approach based on genetic material modification. Its core principle is to deliver functional genetic material to target cells to correct abnormal gene expression or compensate for genetic defects, thereby achieving molecular level intervention at the root of the disease. In the field of tumor treatment, this technology system mainly relies on carrier systems to achieve targeted delivery of therapeutic genes, exerting therapeutic effects through multiple mechanisms such as regulating oncogene expression, repairing mutation sites, blocking malignant proliferation signaling pathways, and enhancing the responsiveness of cytotoxic drugs. Compared to conventional chemotherapy and radiation therapy, this precision medicine model exhibits significant biological advantages: its target has high specificity, which can effectively distinguish between lesions and normal tissues, while significantly reducing the incidence of systemic toxic side effects [1]. At present, this technology has made breakthrough progress in clinical practice of solid tumors and hematological malignancies, providing an important direction for the innovation of tumor treatment paradigms.

Gene therapy, as a cutting-edge and promising medical approach, is gradually changing our traditional understanding of disease treatment. It is based on genetic engineering technology and aims to correct or compensate for diseases caused by genetic defects and abnormalities by introducing exogenous genes, thereby achieving therapeutic goals. This revolutionary treatment method directly targets the root cause of the disease - abnormal genes themselves, rather than just relieving the symptoms of the disease. Its core lies in "gene replacement" or "gene repair". By using specific gene transfer techniques, exogenous normal genes or therapeutic genes are precisely introduced into the target cells of patients. These exogenous genes are expressed in target cells and produce proteins or other molecules with therapeutic effects, thereby replacing or compensating for the function of defective genes, correcting gene abnormalities, and achieving the effect of treating diseases.

2. Strategies for Cancer Gene Therapy

Gene therapy can be divided into two ways from a molecular biology perspective: one is to correct and replace abnormal gene sequences; The second is gene addition and supplementation[2]. The common cancer gene therapy strategies are divided into five categories: suicide gene therapy, gene silencing therapy, tumor suppressor gene therapy, immune system therapy, and anti angiogenic gene therapy.

2.1. Suicide Gene Therapy

The suicide gene intervention strategy in tumor treatment is a precision medical technology based on molecular biology, whose core mechanism is to introduce exogenous drug converting enzyme encoded genes into tumor cells through gene delivery systems. These genes usually originate from microbial specific metabolic pathway related enzyme systems and do not have natural expression characteristics in mammalian cells. When the therapeutic gene is specifically expressed in tumor cells, its product can catalyze the conversion of inactive precursor drugs into active molecules with cytotoxic effects, inducing programmed cell death in malignant cells carrying the gene, thereby achieving selective clearance of tumor lesions. The molecular characteristics of this therapy are reflected in its targeted killing ability against lesion cells. Compared with traditional cytotoxic drugs, its two-stage mechanism of action (gene transduction+prodrug activation) significantly improves the treatment window and reduces adverse effects on normal tissues. The current technology system has demonstrated unique therapeutic advantages in clinical trials of various solid tumors, providing a new technological path for targeted therapy of tumors.

There are currently multiple suicide gene action systems in the field of tumor treatment, mainly including microbial derived enzyme catalytic systems and non-mammalian specific metabolic enzyme systems. From the perspective of mechanism of action, typical representatives include: herpes simplex virus thymidine kinase mediated GCV prodrug activation system, Escherichia coli cytosine deaminase mediated 5-FC conversion system, purine nucleoside phosphorylase catalyzed fludarabine prodrug conversion system, and nitroreductase mediated CB1954 activation system [3]. In addition, the mechanism of carboxypeptidase G2 catalyzing CMDA prodrug conversion and the horseradish peroxidase mediated indole-3-acetic acid activation pathway also exhibit unique functional characteristics. Among numerous technological systems, the two-stage prodrug activation system based on HSV-TK/GCV and CD/5-FC has become the most extensively researched and clinically applied gene therapy strategy in this field due to its clear

molecular mechanism of action and good clinical translation potential.

Technological innovation in the field of cancer treatment targeting suicide gene systems continues to make breakthroughs, with researchers using molecular engineering techniques to perform multidimensional optimization of HSV-TK and CD systems. In the field of TK gene function visualization research, the Shao team developed a quantum dot based nanoprobes technology, which dynamically tracks the gene therapy process by constructing a covalent coupling system between near-infrared fluorescent quantum dots and thymidine kinase genes[4]. This innovative labeling technology not only maintains the optical properties of quantum dots and the biological activity of TK enzymes, but also successfully establishes a full cycle monitoring platform from in vitro experiments to in vivo treatment, providing a new molecular imaging tool for analyzing the mechanism of suicide gene action. Another groundbreaking study came from Lee's team, which constructed a TK-CD dual suicide gene co expression system using a retroviral replication vector and conducted clinical translational studies in 7 patients with glioblastoma[5]. Experimental data shows that the transduction efficiency of therapeutic genes in tumor tissues is significantly positively correlated with the sensitivity of ganciclovir/5-fluorocytosine prodrug, as confirmed by flow cytometry quantitative analysis and high connotation imaging technology. This dual gene system not only inhibits tumor cell proliferation and angiogenesis through synergistic effects, but also significantly enhances the apoptosis rate of in situ transplant tumor models. Its mechanism of action involves multi-target signaling pathway regulation, providing an important technical pathway for improving the clinical efficacy of suicide gene therapy.

Suicide gene therapy, as one of the main methods of tumor gene therapy, overcomes the biggest drawback of virus mediated gene therapy due to its bystander effect: the transduced genes cannot enter all tumor cells. This therapy has shown potential clinical application prospects and value.

2.2. Gene Silencing Therapy

The gene expression regulation technology in tumor treatment, especially the targeted silencing strategy based on RNA interference (RNAi), has become an important research direction in the field of molecular biology. This technology introduces double stranded RNA (dsRNA) into host cells through specific delivery pathways, involving genetic material modification, transposon systems, or virus vector mediated gene delivery processes, ultimately achieving specific inhibition of gene expression[6,7].From a molecular perspective, this regulatory effect mainly occurs in three key stages: genomic DNA transcription initiation stage, mRNA processing maturation stage, and protein translation stage. In theory, by designing small interfering RNA (siRNA) sequences rationally, this technology can achieve precise regulation of any pathogenic gene in the body, opening up a new dimension for molecular targeted therapy of diseases such as malignant tumors. In clinical translational research, Pang et al. systematically revealed the molecular association between microRNA-628 expression levels and the occurrence and development of gastric malignant tumors by constructing specific siRNA probes[8]. Experimental data shows that when the expression of miR-628 gene is inhibited, its low expression state is significantly correlated with the lymphatic metastasis ability, tissue infiltration depth, and TNM clinical staging of gastric cancer lesions. This discovery not only confirms the application value of RNAi technology in tumor molecular typing, but also provides a theoretical basis for the development of precise treatment strategies based on microRNA regulation.

The gene silencing technology based on RNA interference has demonstrated unique molecular therapeutic advantages in the field of tumor treatment. Through the post transcriptional regulation mechanism mediated by exogenous double stranded RNA, this technology can achieve specific inhibition of target genes without affecting the stability of the host genome. Its functional characteristics are mainly reflected in three dimensions: firstly, siRNA molecules exert their effects through epigenetic regulation mechanisms, avoiding direct intervention in chromosomal DNA and significantly reducing the potential risk of inducing gene mutations; Secondly, this technology has high selectivity for target genes and low biological toxicity, making it less likely to cause multidrug resistance issues; Furthermore, precise design of siRNA sequences can simultaneously regulate multiple cancer-related signaling pathways, thereby inhibiting tumor progression. However, it should be noted that this technology mainly acts on gene expression regulation and cannot directly correct genetic material abnormalities[9]. At the clinical application level, siRNA therapy requires the use of delivery systems to overcome biological barriers. Due to the susceptibility of free siRNA molecules to physiological processes such as nuclease degradation, renal clearance, and immune phagocytosis, it is difficult to achieve systematic administration. At present, representative delivery systems in clinical translational research include the CALAA-01 nanoparticle system for melanoma and the ALN-VSPOI composite carrier for the treatment of liver cancer and solid tumors. These systems significantly improve the stability and targeted delivery efficiency of siRNA through molecular encapsulation technology[10,11]. However, it should be noted that the biocompatibility limitations and insufficient intracellular release efficiency of existing delivery vehicles have led to a need to improve the success rate of clinical translation[12].

2.3. Tumor Suppressor Gene Therapy

Tumor suppressor genes play a crucial role in regulating cellular homeostasis. These genes maintain normal physiological functions in specific tissue types, but are often inactivated or lost in expression due to genetic variations in corresponding malignant lesions[13]. At the molecular level, introducing wild-type genes into diseased tissues through delivery systems can induce programmed cell death in tumor cells. More than 20 gene groups with tumor suppressive functions have been identified, including APC genes involved in Wnt signaling regulation, key DNA damage response factor ATM, chromatin remodeling complex component ARID1A, and broad-spectrum tumor suppressor gene p53. Gene replacement therapy, as an important strategy for precision treatment of tumors, is based on the core principle of introducing wild-type tumor suppressor genes into malignant cells through viral or non viral vectors, aiming to correct gene function loss or abnormal expression, and thereby reverse the malignant phenotype. At present, candidate genes that have been extensively studied include p53, which regulates cell cycle progression, Rb, a susceptibility gene for retinoblastoma, and p16INK4A, a cycle dependent kinase inhibitor. These genes have shown

significant potential in restoring normal cell proliferation regulation.

In the field of tumor molecular biology, the p53 gene is the most extensively studied tumor suppressor, and its encoded product serves as a sequence specific transcriptional regulatory protein that can specifically bind to regulatory elements of cell cycle dependent kinase inhibitors. Clinical pathological data shows that in various human malignant tumor cell lines, this gene is often functionally inactivated due to point mutations or structural variations, and more than half of the occurrence and development of malignant tumors are closely related to p53 gene abnormalities. It is worth noting that the mutation hotspots of this gene mainly occur at positions C175, 248, and 282 in the DNA binding domain, and amino acid residue variations in these key regions will directly disrupt its transcriptional regulatory function. To improve the accuracy of gene therapy strategies, researchers continue to optimize the design of delivery systems. The novel nuclear targeted co delivery system developed by Lin et al. is representative, which utilizes an acylated modified HIV-1 transcription activator (TAT) functionalized chitosan poly-N-3-carboxybenzyloxylysine (CCL) composite carrier to successfully achieve synergistic delivery of wild-type p53 gene and doxorubicin[14]. Experimental data shows that this system not only breaks through the intracellular transport barrier of traditional carriers, but also significantly improves the transfection efficiency of therapeutic genes and the targeted accumulation ability of chemotherapy drugs through nuclear localization advantages, demonstrating a synergistic effect in inhibiting tumor proliferation.

At present, researchers are still continuously discovering new tumor suppressor genes, such as KLF6, ING4, NOL7, ARLTS1, Runx3, etc[15,16]. Due to the fact that these tumor suppressor genes were discovered during the study of a single tumor, they may not necessarily have inhibitory effects on other tumors. Even the p53 gene, which has broad-spectrum tumor suppressor properties, has shown significant therapeutic effects on certain tumors in clinical stages I/II, but its clinical efficacy in stage III still needs to be observed. Therefore, further research is needed to determine which tumor suppressor gene is most effective for different types of tumors.

2.4. Immune System Therapy

The immune system is a key factor in the disappearance or spread of cancer, and immunotherapy for cancer can be divided into four categories: active immunotherapy, passive immunotherapy, adoptive immunotherapy, and immune enhancement therapy [17]. Immunotherapy may include one or more of the aforementioned methods as a unique immunotherapy treatment, or in combination with other cancer therapies.

2.4.1. Active Immunotherapy

The active regulatory strategy in tumor immunotherapy activates the host immune system's ability to recognize tumor associated antigens through a specific antigen presentation mechanism, with typical representatives including biological agents such as tumor vaccines. The Wolff team innovatively developed a DNA vaccine construction technology based on exogenous transcription factor antigens[18]. Through genetic engineering, plasmids encoding tumor specific antigens are introduced into host cells, and after transcription and translation, antigen peptides are generated to activate T cell-mediated cellular immunity and B cell-dominated humoral immune responses. Compared to viral vectors or bacterial delivery systems, this vaccine system has higher biosafety features: it not only avoids the risk of pathogen infection, but also significantly reduces the probability of inducing autoimmune abnormalities. At the same time, its standardized production process is more in line with industrial needs[19]. However, it should be noted that there is a time-dependent decay in the immune response, and the therapeutic effect needs to be maintained through periodic immune enhancement programs.

2.4.2. Passive Immunotherapy

The passive intervention strategy in tumor immunotherapy achieves specific recognition of tumor antigens through genetically engineered antibodies, and its mechanism of action does not rely on direct activation of the host immune system. Typical representatives of this treatment model include a number of targeted therapeutic biological agents approved by FDA: trastuzumab for breast cancer HER2/neu target, rituximab, an inert lymphoma CD20 antigen antagonist, cetuximab, an epidermal growth factor receptor antagonist for lung cancer, and bevacizumab, a vascular endothelial growth factor inhibitor widely used in the treatment of solid tumors[20-23]. In recent years, antibody drug conjugates (ADCs) have made breakthrough progress as a novel targeted therapy system. Their structure is composed of monoclonal antibodies coupled with highly efficient cytotoxic molecules through cleavable linkers. This innovative design combines the targeted recognition ability of antibodies with the potent killing properties of small molecule drugs, significantly improving the treatment window[24]. At present, ADC drugs have demonstrated excellent efficacy in the treatment of hematological and solid tumors, becoming an important development direction in the field of precision medicine.

2.4.3. Adoptive Immunotherapy

Adoptive immunotherapy utilizes the patient's immune cells, whether T cells or dendritic cells, to be stimulated or manipulated in vitro, and then injected back into the body to better combat cancer antigens. Hinrichs et al. collected cancer infiltrating T lymphocytes from patients with metastatic cervical cancer induced by human papillomavirus (HPV) and infused them into their bodies[25]. The researchers subsequently detected an increase in the expression level of interleukin-2 in the patients' bodies, and half of the patients had a decrease in cancer volume. Among them, two patients had complete cancer regression after 18 and 11 months of treatment, and the body had almost no side effects.

2.4.4. Immunoenhancement Therapy

The regulatory intervention strategies in tumor immunotherapy focus on reprogramming the immune microenvironment, with the core mechanism involving activation of co stimulatory signaling pathways and blockade of inhibitory molecular pathways. In recent years, significant clinical breakthroughs have been made in immune checkpoint inhibitors targeting programmed death receptor 1 (PD-1) and its ligand PD-L1[26]. A typical case is the development of Septizumab by Regenerative Element Company. This fully humanized monoclonal antibody specifically blocks the interaction between PD-1/PD-L1 molecules, relieving T cell functional inhibition and enhancing the body's anti-tumor immune response. On September 28, 2018, it was approved by the US Food and Drug Administration (FDA) for the treatment of unresectable or radiation resistant metastatic

squamous cell carcinoma. On June 28 of the following year, it was certified by the European Medicines Agency (EMA), becoming the first PD-1 inhibitor approved for the treatment of advanced squamous cell carcinoma and the third anti-PD-1 monoclonal antibody drug approved by the FDA for marketing[27]. The clinical translation of this drug marks an important progress in the field of immune checkpoint therapy for solid tumors.

2.5. Antiangiogenic Gene Therapy

The imbalance of angiogenesis regulatory network in the microenvironment of malignant tumors is an important pathological feature driving tumor progression, which essentially lies in the vicious cycle of abnormal activation of pro angiogenic signaling pathways and functional inactivation of inhibitory regulatory factors. At the molecular level, the overexpression of pro angiogenic factors such as vascular endothelial growth factor (VEGF) and the low expression of anti angiogenic factors form a dynamic imbalance, leading to intensified pathological angiogenesis and promoting tumor cell proliferation, metastasis, and diffusion. The treatment strategy for this pathological mechanism needs to break through the limitations of traditional pharmacokinetics. Gene therapy can achieve sustained and stable release of therapeutic inhibitory factors through endogenous expression regulation systems, maintaining the optimal therapeutic concentration threshold in the tumor site. This genetic engineering based technological pathway not only overcomes the shortcomings of short half-life and high systemic toxicity of conventional anti angiogenic drugs, but also accurately regulates the angiogenesis regulatory network in the tumor microenvironment, providing innovative solutions for anti angiogenic therapy.

Pathological angiogenesis in the tumor microenvironment is precisely regulated by multiple signaling pathways, among which the vascular endothelial growth factor (VEGF) family and its tyrosine kinase receptors (VEGFR-1/FLT-1, VEGFR-2, VEGFR-3/FLT-4) and the angiopoietin family and its receptors (Tie1/Tie2) form the core biological regulatory network[28]. This pathway has important research value in the field of tumor treatment, and has become an intervention target for both monotherapy and combination therapy. In clinical practice, molecular inhibitors targeting the VEGFR signaling pathway such as regorafenib, famotinib, axitinib, and apatinib have been proven to have significant therapeutic effects on metastatic colorectal cancer. At the level of gene therapy, researchers developed an anti angiogenic strategy based on adenovirus vectors in 2012. By expressing soluble VEGF bait receptors (-1, -2, -3 types) lacking tyrosine kinase domains, it was demonstrated in mouse tumor models that combined gene therapy has stronger anti-tumor effects than single gene intervention[29]. Its mechanism of action involves blocking the VEGFR signaling pathway through competitive binding, while inhibiting multidimensional pro angiogenic signals. Further research has found that when chemotherapy drugs such as paclitaxel (PTX) are introduced into combination therapy, the survival rate of experimental animal models can be significantly improved, indicating that multimodal combination intervention has synergistic potential in tumor vascular targeted therapy[30].

Antiangiogenic gene therapy is different from conventional therapy and other gene therapies, as it has many advantages such as high efficacy, low toxicity, low susceptibility to drug resistance, and is not affected by the tumor cell cycle. Therefore, there will be broad application prospects in the treatment of tumors and other vascular diseases.

3. Application of Gene Therapy for Cancer

Gene therapy for cancer has the advantages of strong targeting and wide therapeutic effect, which is widely used in the treatment of lung cancer, liver cancer, breast cancer, leukemia and other diseases. The following typical applications are given as examples.

3.1. Adenovirus Mediated p53 Gene Therapy for Bladder Cancer

Bladder cancer is a common malignant tumor of urinary system, 90% of which is transitional cell carcinoma (TCC). The 5-year recurrence rate of transurethral bladder tumor resection (TURBT) is as high as 70%, and adjuvant chemotherapy has problems such as high adverse reactions and drug resistance. Research has shown that approximately 40% to 50% of TCC patients have p53 gene mutations (mt-p53), which lead to loss of tumor suppressor function and promote tumor progression. Therefore, restoring wild-type p53 (wt-p53) function through gene therapy has become a potential therapeutic strategy.

The p53 gene is located at 17p13.1 and encodes a key protein that regulates cell cycle, DNA repair, and apoptosis. It is known as the "guardian of the genome"; WT-P53 induces G1 phase arrest to repair DNA damage by activating p21, or induces irreversible cell apoptosis through pro apoptotic proteins such as Bax and PUMA; Mt-p53 loses its tumor inhibiting function, promotes tumor invasion, metastasis and chemotherapy resistance, and is associated with poor prognosis of bladder cancer[31].

Therefore, adenovirus mediated p53 gene therapy has demonstrated good safety and efficacy by restoring the regulatory mechanism of tumor cell apoptosis, especially when combined with chemotherapy, which can synergistically enhance efficacy. Despite the challenges of immune response and targeting, it has broad prospects as a new treatment for bladder cancer.

3.2. Modification of Autologous Lymphocytes for The Treatment of Skin Cancer

The team from the American Cancer Institute conducted experiments on 17 patients with advanced melanoma. They genetically engineered autologous T lymphocytes from patients, extracted normal lymphocytes from their bodies, modified them in vitro using viruses carrying T cell receptor genes, amplified them to billions, and then transfused them back into patients' bodies to express receptors that specifically recognize cancer cells. The modified T cells in 15 patients survived and slowly proliferated, with 2 patients experiencing complete tumor regression and disease-free survival exceeding 1 year.

This study confirmed for the first time that genetic engineering cell therapy can induce the regression of advanced cancer, providing new ideas for the treatment of breast cancer, lung cancer and other cancers. It is a major breakthrough in cancer research using gene technology, bringing new hope for the cure of cancer to humanity[32].

3.3. Acoustic Pore Effect Therapy for Cancer Treatment

Based on the latest research results in the Proceedings of the National Academy of Sciences, an important technological breakthrough has been made in the field of physical targeted delivery systems - a new gene delivery strategy that integrates ultrasound energy and microbubble technology, opening up a new dimension for the treatment of major diseases. The acoustic pore effect therapy developed by a research team at the University of Pittsburgh induces microbubble cavitation by precisely regulating ultrasound field parameters, achieving reversible changes in cell membrane permeability. This technology breaks through the limitations of traditional gene delivery techniques and demonstrates unique advantages in the treatment of cardiovascular diseases and malignant tumors: its mechanism of action achieves transmembrane transport of gene carriers through acoustic mechanical effects, while maintaining cell activity and functional integrity. Research data show that this non-invasive physical delivery system can significantly improve the transfection efficiency of therapeutic genes, and its precise spatiotemporal control characteristics are more conducive to targeted intervention at the lesion site. At present, breakthroughs have been made in preclinical research such as atherosclerotic plaque ablation and solid tumor microenvironment regulation.

The shear stress threshold caused by a microbubble oscillation is approximately 1 kPa, and when the pressure exceeds this value, the permeability of the endothelial cell membrane increases. The shear stress threshold shows an inverse square root relationship with the number of oscillation periods and ultrasound frequencies ranging from 0.5 to 2.0 Hz. In addition, measurements using real-time 3D confocal microscopy have shown that a process of acoustic pore effect is directly caused by the encapsulation of the top and base cell membranes along their outer sides (sealing time<2 min), leading to the immediate generation of membrane pores in the cells. The acoustic pore effect also has great potential in cell fusion, as it can allow two adjacent cells to fuse within 30-60 minutes.

Using ultrasound energy and small bubbles, selectively opening a small hole on the cell for drug delivery. By using focused ultrasound beams, drugs can be accurately delivered to the affected area while preserving healthy tissue.

4. Conclusion

Advances in high-throughput sequencing and CRISPR gene editing have propelled transformative developments in tumor gene therapy. Contemporary molecular therapeutic frameworks now integrate a translational research pathway encompassing molecular regulation, cellular remodeling, and systemic intervention. The three-tiered strategy comprises: (1) Genetic-level interventions utilizing gene editing for precise mutation correction or epigenetic modulation of tumor suppressor genes; (2) Cellular-level engineering of immune effector cells to optimize tumor targeting capabilities; (3) Microenvironmental modifications through multimodal approaches targeting pathological angiogenesis and cytokine network reprogramming. These innovations have established a comprehensive technical matrix spanning gene silencing, replacement therapy, and immune microenvironment regulation, substantially enhancing treatment precision and therapeutic durability.

Despite clinical progress, critical scientific challenges persist in tumor gene therapy. Key biological limitations manifest in three domains: First, tumor genetic heterogeneity complicates targeted interventions, necessitating highly individualized genomic profiling. Second, the multigenic nature of tumorigenesis involving cross-talking signaling pathways renders single-gene modulation insufficient for complete tumor eradication. Third, dynamic variations in host immune microenvironments contribute to significant interpatient therapeutic response disparities. These biological complexities underscore the imperative for developing multi-target synergistic intervention strategies to overcome therapeutic resistance barriers, particularly in managing advanced malignancies.

References

[1] Yang, L., Huang, C., Wang, M. (2020) Advances in Gene Therapy for Cancer. J. Sci. Commun., 3: 001.

[2] Liu, J. (2006) The Strategy of Cancer Gene Therapy. J. Sci. Commun., 3: 179–186.

[3] Navarro, S.A., Carrillo, E., Grinan-Lison, C., et al. (2016) Cancer suicide gene therapy: a patent review. Expert Opin. Ther. Pat., 26: 1095–1104.

[4] Shao, D., Li, J., Xiao, X., et al. (2014) Real-time visualizing and tracing of HSV-TK/GCV suicide gene therapy by near-infrared fluorescent quantum dots. ACS Appl. Mater. Interfaces, 6: 11082–11090.

[5] Lee, M., Kim, Y.S., Lee, K., et al. (2019) Novel Semi-Replicative Retroviral Vector Mediated Double Suicide Gene Transfer Enhances Antitumor Effects in Patient-Derived Glioblastoma Models. Cancers, 11: E1090.

[6] Gujrati, M., Lu, Z.R. (2014) Targeted Systemic Delivery of Therapeutic siRNA. Gene Ther. Cancer, 3: 51–59.

[7] Sato, Y., Murase, K., Kato, J., et al. (2008) Resolution of liver cirrhosis using vitamin A-coupled liposomes to deliver siRNA against a collagen-specific chaperone. Nat. Biotechnol., 26: 431–442.

[8] Pang, W., Zhai, M., Wang, Y., et al. (2019) Long noncoding RNA SNHG16 silencing inhibits the aggressiveness of gastric cancer via upregulation of microRNA-628-3p and consequent decrease of NRP1. Cancer Manag. Res., 11: 7263–7277.

[9] Singh, A., Trivedi, P., Jain, N.K. (2018) Advances in siRNA delivery in cancer therapy. Artif. Cells Nanomed. Biotechnol., 46: 274–283.

[10] Davis, M.E. (2009) The first targeted delivery of siRNA in humans via a self-assembling, cyclodextrin polymer-based nanoparticle: from concept to clinic. Mol. Pharm., 6: 659–668.

[11] Tabernero, J., Shapiro, G.I., LoRusso, P.M., et al. (2013) First-in-humans trial of an RNA interference therapeutic targeting VEGF and KSP in cancer patients with liver involvement. Cancer Discov., 3: 406–417.

[12] Fung, H., Gersson, S. (2014) Viral insertion site detection and analysis in cancer gene therapy. Gene Ther. Cancer, 3: 35–46.

[13] Deng, Y., Zhao, Y., Cheng, F., et al. (2014) The latest research progress of tumor suppressor gene NDRG2. J. Mod. Oncol., 4: 962–965.

[14] Lin, J., Chen, H., Wang, D., et al. (2019) Nuclear-targeted p53 and DOX co-delivery of chitosan derivatives for cancer therapy in vitro and in vivo. Elsevier, 183: 114–137.

[15] Lievre, A., Landi, B., Cote, J.F., et al. (2005) Absence of mutation in the putative tumor-suppressor gene KLF6 in colorectal cancers. Oncogene, 24: 7253–7256.

[16] Guo, C., Ding, J., Yao, L., et al. (2005) Tumor suppressor gene Runx3 sensitizes gastric cancer cells to chemotherapeutic drugs by downregulating Bcl-2, MDR-1 and MRP-1. Int. J. Cancer, 116: 155–160.

[17] Reardon, D.A., Wucherpfennig, K.W., Freeman, G., et al. (2013) An update on vaccine therapy and other immunotherapeutic approaches for glioblastoma. Expert Rev. Vaccines, 12: 597–615.

[18] Wolff, J.A., Budker, V. (2005) The mechanism of naked DNA uptake and expression. Adv. Genet., 54: 3–20.

[19] Lopes, A., Vandermeulen, G., Préat, V. (2019) Cancer DNA vaccines: current preclinical and clinical developments and future perspectives. J. Exp. Clin. Cancer Res., 38: 146.

[20] Lambertini, M., Pondé, N.F., Solinas, C., et al. (2017) Adjuvant trastuzumab: a 10-year overview of its benefit. Expert Rev. Anticancer Ther., 17: 61–74.

[21] Salles, G., Barrett, M., Foà, R., et al. (2017) Rituximab in B-Cell Hematologic Malignancies: A Review of 20 Years of Clinical Experience. Adv. Ther., 24: 2232–2273.

[22] Park, T., Choi, C.J., Choi, Y., et al. (2016) Cost-effectiveness of cetuximab for colorectal cancer. Expert Rev. Pharmacoecon. Outcomes Res., 16: 667–677.

[23] Diaz, R.J., Ali, S., Qadir, M.G., et al. (2017) The role of bevacizumab in the treatment of glioblastoma. J. Neurooncol., 133: 455–467.

[24] Yaghoubi, S., Karimi, M.H., Lotfinia, M., et al. (2019) Potential drugs used in the antibody-drug conjugate (ADC) architecture for cancer therapy. J. Cell. Physiol., 234: 1–34.

[25] Hinrichs, C.S., Stevanović, S., Draper, L., et al. (2014) HPV-targeted tumor-infiltrating lymphocytes for cervical cancer. Clin. Oncol., 32: 233–245.

[26] Guzik, K., Zak, K.M., Grudnik, P., et al. (2017) Small-Molecule Inhibitors of the Programmed Cell Death-1/Programmed Death-Ligand 1 (PD-1/PD-L1) Interaction via Transiently Induced Protein States and Dimerization of PD-L1. J. Med. Chem., 60: 5857–5867.

[27] Ahmed, S.R., Petersen, E., Patel, R. (2019) Cemiplimab-rwlc as first and only treatment for advanced cutaneous squamous cell carcinoma. Expert Rev. Clin. Pharmacol., 12: 1–5.

[28] Lin, X., Khalid, S., Qureshi, M.Z., et al. (2016) VEGF mediated signaling in oral cancer. Cell. Mol. Biol., 62: 64–68.

[29] Sopo, M., Anttila, M., Sallinen, H., et al. (2012) Antiangiogenic gene therapy with soluble VEGF-receptors -1, -2 and -3 together with paclitaxel prolongs survival of mice with human ovarian carcinoma. Cancer, 131: 2394–2401.

[30] Tuppurainen, L., Sallinen, H., Kokki, E., et al. (2013) Preclinical safety, toxicology, and biodistribution study of adenoviral gene therapy with sVEGFR-2 and sVEGFR-3 combined with chemotherapy for ovarian cancer. Hum. Gene Ther. Clin. Dev., 24: 29–37.

[31] Shi, X., Cheng, Y. (2009) Gland virus mediated P53 gene to treat bladder cancer. J. Cancer Res. Ther., 1: 180–184.

[32] Li, W. (2006) Modifying autologous lymphocyte genes are expected to treat skin cancer. Foreign Med. Sci., 10: 27–28.