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*REVIEW*

# Gene therapy for gastric cancer: Is it promising?

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## Abstract

Gastric cancer is one of the most common tumors worldwide. The therapeutic outcome of conventional therapies is inefficient. Thus, new therapeutic strategies are urgently needed. Gene therapy is a promising molecular alternative in the treatment of gastric cancer, including the replacement of defective tumor suppressor genes, the inactivation of oncogenes, the introduction of suicide genes, genetic immunotherapy, anti-angiogenetic gene therapy, and virotherapy. Improved molecular biological techniques and a better understanding of gastric carcinogenesis have allowed us to validate a variety of genes as molecular targets for gene therapy. This review provides an update of the new developments in cancer gene therapy, new principles, techniques, strategies and vector systems, and shows how they may be applied in the treatment of gastric cancer.



**Key words:** Gene therapy; Gastric cancer; Virotherapy

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## INTRODUCTION

Gastric cancer is the fourth most common malignancy worldwide with an estimated 934 000 new cases that was reported in 2002 and the second most common cause of death from cancer (700 000 deaths annually). Almost two-thirds of the cases occur in developing countries and 42% in China alone[1]. The prognosis of gastric cancer is poor with an estimated relative 5-year survival rate of less than 20%[2]. The efficacy of current therapeutic approaches such as surgery, hormone, radio- and chemotherapy is limited. Thus, new therapeutic approaches are urgently needed. Cancer is an acquired genetic disease developing in a multi-step process. Mutations of genes related to growth control, apoptosis, invasion and metastasis form the molecular genetic basis of malignant transformation and tumor progression[3]. The characterization of dysregulated genes like the tumor suppressor p53, which are critical for carcinogenesis, and a better understanding of the molecular basis for tumor-host interaction led to significant progress in the development of new therapeutic agents. More than 15 years ago, gene therapy emerged as a new therapeutic approach and has meanwhile become an important strategy in cancer treatment. Cancer is by far the most frequent of all indications addressed by gene therapy (60% of all clinical trials[3]), underlining the expectations raised by this new therapeutic option. The original concept of cancer gene therapy was further developed into two branches as a result of different strategies of therapeutic benefit: molecular cancer therapy and virotherapy. Molecular cancer therapy can be defined as a therapeutic technique, which aims at the introduction of nucleic acids into cancer patients' cells in order to modulate the gene expression profile of the target cells and thereby eradicate the tumor[4]. In contrast, virotherapy is a new concept of gene therapy that uses replication-competent oncolytic viral vectors (OVV) with viro-oncolytic potency for targeted tumor cell destruction[5].

There are different ways to modulate tumor growth by gene therapeutic strategies. These include direct destruction of tumor cells, inhibition of tumor angiogenesis and tumor cell spread and activation of the host immune response against the tumor. Although all these approaches showed promising anti-tumor effects in pre-clinical investigations, clinical trials have often been disappointing, since they demonstrated only slight therapeutic benefit. Thus, a major breakthrough is still needed in gene therapy of cancer. Nevertheless, clinical trials proved the relative safety of human cancer gene therapy. The application of vectors and the expression of transgenes are generally well tolerated and the low risk of severe side effects seems to be calculable.

The main problem of the relative inefficiency of cancer gene therapy continues to be the low *in vivo* efficiency of gene delivery into the target tumor cells, leading to low expression of therapeutic genes and thus limited curative effects. Several factors seem to be responsible for this, among them the presence of anatomic barriers inhibiting the efficient transfer of vectors from circulation to target cells and the low expression of vector-specific target receptors on the cancer cells causing reduced

cellular uptake of viral vectors. Moreover, immunological responses of the host against the vectors and the rapid clearance of vectors from circulation after intravascular administration may be important factors preventing efficient gene transfer[6-8]. In the last few years, great efforts have been made to overcome these limitations. Especially the development of OVV[9] and vectors with enhanced tumor-specific targeting[10,11] together with improved vector application protocols have led to a significant enhancement of vector-mediated gene delivery. Furthermore, the use of new powerful molecular techniques like RNA interference (RNAi)[12] and the detection of new target genes are hopeful signs for improving human cancer by gene therapy. In the present paper, we review new trends in gene therapy and update their application in gastric cancer.

## TUMOR SUPPRESSOR GENES

The most obvious way to target growth regulation in cancer cells is to introduce tumor suppressors that may be inactivated in tumors. The replacement of p53, which is the most commonly inactivated tumor suppressor and mutated in about 60% of human gastric cancers, has emerged as an attractive treatment option, both alone and combined with conventional chemotherapy[13,14]. Introduction of the p53 gene via a recombinant adenovirus has been shown to inhibit the growth of gastric cancer cells with mutated p53 *in vitro* and *in vivo*[15,16]. The pro-apoptotic function of p53 depends on the transactivation of genes such as Bax, Apaf-1, Fas, and PTEN, whose own expression or activity may be abnormal in tumor cells[17]. Consequently, the Bax gene may serve as a good alternative to p53 for cancer gene therapy, not only because it has been shown to kill cancer cells irrespective of their p53 status, but also because it may increase their sensitivity to other anti-tumor treatments[18]. Moreover, the adenoviral expression of the initiator caspase-8 leads to the selective induction of apoptosis in detached gastric tumor cells *in vitro* and *in vivo*, thus displaying anti-metastatic potential in gastric cancer[19]. All these signaling molecules work through a common pathway involving activation of the effector caspase 3. Thus, recombinant expression of caspase 3 leads to the induction of apoptosis in gastric cancer cells[20]. Moreover, the introduction of wild-type p16INK4A, another tumor suppressor and cell cycle regulator in gastric cancer cells harboring a p16 mutation, may also be a feasible approach to efficient tumor growth control and chemosensitization[21]. Finally, the replacement of Fhit, a tumor suppressor often inactivated in gastric cancer, decreases sensitivity to carcinogens and induces apoptosis in gastric tumor cells *in vivo*. Therefore, restoring Fhit expression by viral transduction may be a promising strategy for both the prevention and therapy of gastric tumors[22].

## SUICIDE GENES

This strategy relies on the conversion of non-toxic substances (prodrugs) into physiologically active agents by means of non-mammalian enzymes. These suicide enzymes are over-expressed in neoplastic cells as a result of successful transfection with their genes[23]. The most widely used suicide gene/prodrug system is the herpes simplex virus (HSV) thymidine kinase (HSV-tk)/ganciclovir (GCV) system that can convert the prodrug GCV into phosphorylated GCV. The phosphorylated GCV inhibits cellular DNA synthesis and leads to the killing of cancer cells via apoptotic and non-apoptotic mechanisms[24,25]. One of the powerful features in these systems is the "bystander effect", the mechanism by which the toxic metabolites are transferred from transduced cells to neighboring cancer cells via gap junctions or apoptotic vesicles. The bystander effect drastically enhances the tumor-killing capacity of the HSV-tk/GCV system[26,27]. Several studies were undertaken to evaluate the potential of suicide gene therapy in gastric cancer. In alpha-fetoprotein (AFP)-producing gastric tumors, the adenovirus-mediated expression of HSV-tk by an AFP enhancer/promoter element selectively eliminated AFP-positive, but not AFP-negative cell lines when treated with ganciclovir[28]. This approach may be a promising tumor-selective treatment option for AFP-positive gastric tumors with a very poor prognosis. A similar approach involves the expression of recombinant *E. coli* cytosine deaminase (CD) in gastric cancer cells together with the administration of 5-fluorocytosine (5-FC). 5-FC is given orally and converted to 5-fluorouracil in the tumor cells expressing CD. In attempts to increase the specificity of suicide gene therapy, CD expressed from gastric cancer cell-specific promoters SEL1L and TP1 was shown to cause efficient cytotoxic effects in combination with 5-FC[29]. An earlier attempt with tumor-specific and more efficient CD/5-FC gene therapy was carried out using the Cre/loxP regulation system. Ueda *et al*[30] constructed an adenovector-expressing Cre recombinase from a carcinoembryonic antigen (CEA) promoter and a second vector expressing CD under the control of the CAG promoter. The double infection with both vectors rendered CEA-producing gastric cancer cells 13 times more sensitive to 5-FC than the single infection with a vector expressing CD from the CEA promoter. Consequently, anti-tumor efficacy *in vivo* was also significantly enhanced by using the Cre/loxP system compared to the single infection with the vector directly expressing CD under the control of the CEA promoter. Finally, recombinant expression of the bacterial enzyme nitroimidazole reductase gene together with the administration of the prodrug CB1954 was evaluated in a phase I and pharmacokinetic study with the intention of treating gastric cancer[31].

## ANTI-ANGIOGENESIS GENE THERAPY

Tumor angiogenesis plays an important role in the growth of solid tumors and the formation of metastases. Angiogenesis is a multi-level process including endothelial cell proliferation, migration, basement membrane degradation, and lumen reorganization. It is stimulated by several factors secreted from both host and tumor cells. The principal growth factors driving angiogenesis include, among others, the vascular endothelial growth factor (VEGF), the basic fibroblast growth factor, and the hepatocyte growth factor (HGF)[32]. Thus, there are various

potential targets for anti-angiogenic cancer gene therapy. In contrast to other genetic treatments, anti-angiogenic gene therapy does not necessarily require direct and selective transduction of target genes into cancer cells, but rather transduction around the tumor to create an anti-angiogenic environment[33]. This advantage helps to overcome the limitations of the currently available vector systems, which often lack adequate transduction efficiency in cancer cells. Several studies were undertaken to evaluate the potential of anti-angiogenic gene therapy in gastric cancer. One study demonstrated that, if expressed from adenovector-transduced peritoneal mesothelial cells, the soluble VEGF receptor sFlt-1 is able to inhibit the peritoneal dissemination of gastric cancer *in vivo* and consequently prolong the survival of treated animals[33]. Another study evaluated the therapeutic efficacy of the HGF antagonist NK4, which is known for its inhibitory effects on several angiogenetic pathways. Application of an NK4-expressing adenovector inhibited the formation of both peritoneal metastases and intra-tumor vessels in gastric cancer *in vivo*[34]. New potential targets for anti-angiogenic gene therapy of gastric cancer were recently discovered. Meng *et al*[35] and Xue *et al*[36] showed that silencing Raf-1 and Rac1 GTPase, which are critical factors in hypoxia-induced gene activation of several angiogenesis factors, results in downregulation of the angiogenesis-promoting factors VEGF and Hif-1α and upregulation of the tumor suppressors and angiogenesis inhibitors p53 and VHL. Furthermore, downregulation of Raf-1 and Rac1 GTPase leads to tumor cell apoptosis and significantly inhibits cell proliferation. Similarly, Stoeltzing *et al*[37] showed that direct suppression of Hif-1α resulted in decreased secretion of VEGF, thereby impairing tumor growth, angiogenesis and vessel maturation *in vivo*.

## GENETIC IMMUNOTHERAPY

Genetic immunotherapy aims at improving the host's immune response to a particular tumor and is currently one of the most promising gene therapeutic options for cancer. The function of the immune system is very complex and its activation in gene therapeutic settings can be achieved by employing different strategies[38]. One of the most common strategies in immunotherapy of cancer is the use of mediators of the immune system. Among them, IL-2, IL-12, INF-γ, GM-CSF and TNF-α have raised special attention and several trials have proved their efficacy in cancer gene therapy[39-42]. New developments indicate further improvement of the benefit, if cytokine therapy is combined or used with other gene therapeutic options. For example, synergistic anti-tumor effects were achieved by simultaneous expression of IL-2 and INF-γ[40] or by combining an oncolytic adenovirus (oAdV) with IL-12 immunotherapy[43].

Based on this knowledge, studies were carried out in order to prove the efficacy of immunotherapy in combination with other gene therapeutic strategies in gastric cancer. Zhang *et al*[44-46] evaluated the anti-tumor effects of the HSV-tk/GCV system together with the expression of recombinant IL-2 or TNF-α in gastric cancer. In contrast to their disappointing results *in vitro*[46], they observed enhanced anti-tumor effects by HSV-tk/GCV suicide gene therapy combined with recombinant TNF-α expression *in vivo*[44]. Using a similar protocol, another group found strongly enhanced anti-tumor effects after coexpression of IL-2, GM-CSF and HSV-tk/GCV in a gastric cancer model *in vivo*[47]. These results strongly indicate the potential impact of combined cytotoxic and immunomodulatory gene therapy in gastric cancer. Other immunotherapeutics also demonstrated their potential efficacy in gastric cancer. For example, it was shown that the expression of recombinant intercellular adhesion molecule (ICAM)-2 prolonged the survival of mice with peritoneal metastases of gastric cancer[48]. Meng *et al*[49] tested the recently discovered gastric carcinoma-specific tumor-associated antigen MG7-Ag in a *Salomonella typhimurium* vaccine against gastric cancer. In detail, they constructed a recombinant gene vaccine consisting of the MG7-Ag mimotope fused with HBcAg, a protein from HBV enhancing the immunogenicity of its antigens. Oral application of the vaccine *in vivo* led to increased formation of MG7-Ag antibodies, reduced average tumor weight compared to the controls and prevented tumor growth in one of five immunized mice, thereby indicating some protective effects of the vaccine[50].

## GENE SILENCING APPROACHES

Inappropriately expressed genes are a major cause of uncontrolled cell growth. Thus, the specific downregulation of (onco)gene expression leading to tumor growth inhibition is a promising approach in cancer gene therapy[51]. Several years ago, double-strand RNA molecules homologous to the sequence of the target gene were shown to induce post-transcriptional gene silencing (PTGS) in a sequence-specific manner. This mechanism was designated as RNAi[52]. The process of PTGS is initiated by small interfering (si) RNA molecules, which have a length of 21-23 nucleotides[12]. In mammalian cells, siRNAs are incorporated into a large protein complex, the RNA-induced silencing complex, leading to precise degradation of complementary mRNA targets[53]. Due to its extraordinary efficiency, target gene specificity and simplicity of construction, siRNA technology has gained considerable attention as a new tool for gene knockdown and, hence, therapeutic use in cancer gene therapy. Chemically synthesized or *in vitro*-transcribed siRNAs are widely used for *in vitro* anti-cancer studies, while their use *in vivo* revealed several problems. Major limitations *in vivo* are the generally low transduction efficiency and short half-life. Furthermore, synthetic siRNAs preferentially transduce the liver after systemic application[54], rendering them useless for systemic cancer gene therapy. These obstacles may be overcome by the expression of siRNA from viral vectors. Currently, adenoviral, retroviral and adeno-associated virus vectors have been shown to efficiently express siRNAs resulting in strong downregulation of the target gene[55-57]. In this setting, vector-based expression systems were further developed, enabling tissue-specific and inducible siRNA expression by the use of tissue specific promoters[58] and pharmacologically regulated gene expression systems[55].

Furthermore, siRNA expressed from viral vectors seems to be more stable than synthetic siRNA[59]. Several studies were undertaken to evaluate siRNA technology in gastric cancer. Hong *et al*[60] constructed a eukaryotic vector expressing siRNA against new zinc ribbon (ZNRD1) gene, which promotes a multi-drug resistant phenotype in gastric cancer through the upregulation of permeability-glycoprotein. After transfection of a ZNRD1 siRNA, a dramatic reduction of ZNRD1 was observed accompanied by a significantly enhanced sensitivity to vincristine, adriamycin and etoposide. Further studies proved the high efficiency of siRNA-mediated gene silencing in gastric cancer cells *in vitro*[35,59,61-63]. Continuous development of siRNA technology warrants further investigations of its future therapeutic use in gastric cancer *in vivo*.

Further approaches for the downregulation of tumor genes in gastric cancer, including anti-sense-RNA[64], anti-sense oligonucleotides[65,66], ribozymes[67], and dominant negative forms of tumor proteins[37,68], have also been investigated and may be of potential clinical value in the gene therapy of gastric cancer. While anti-sense strategies preferentially aim at blocking the translation of a target mRNA by complementary binding to its specific mRNA, dominant negative mutant alleles compete with their endogenous homologs for binding in a protein complex, leading to the inhibition of protein function. For example, the insulin-like growth factor (IGF) I receptor is involved in carcinogenesis and proliferation. Its blockade by adenovector-mediated expression of a truncated dominant negative IGF was shown to sensitize gastric tumor cells for chemotherapy and to suppress their peritoneal dissemination *in vivo*[68]. In another study, Kim *et al*[66] showed that downregulation of anti-apoptotic protein bcl-2 by administering bcl-2 anti-sense oligonucleotides significantly increased the sensitivity of gastric cancer to chemotherapeutics *in vivo*.

## VIROTHERAPY

The limited efficiency of replication-deficient viral vectors to transduce cancer cells and express effector genes *in vivo* led to the development of a new vector generation called OVV. In contrast to replication-deficient viral vectors, the primary replication cycle of OVV causes viro-oncolyis of initially infected tumor cells, resulting in the release of progeny virions followed by the infection of adjacent cells and the infection and destruction of further tumor mass[69]. Thus, OVV are intended to ultimately destroy a tumor although only a small percentage of tumor cells was initially infected. Furthermore, progeny virions can spread systemically by circulation[70] and infect tumor cells remote from the primary replication site of OVV, thus enhancing the potential therapeutic efficacy in metastatic cancer.

The restriction of OVV replication to cancer cells is a central concern of OVV development. This aim has been achieved by genetic engineering of viral vector genomes (e.g. in herpes- and adenoviruses) either by driving of viral genes essential for virus replication by tumor-specific promoters[71,72] or by inserting mutations into viral genes that abolish their function for viral replication in normal cells but not in tumor cells[73]. Other OVV with inherent oncolytic potency acquire tumor-selective replication competence through defects or dysregulation of cellular genes in cancer cells (e.g. Newcastle virus and vesicular stomatitis virus)[74,75].

Several studies have demonstrated that replication of OVV is 100- to 1 000-fold attenuated in normal cells compared to cancer cells. As shown in oAdVs, OVV safety can be further increased by pharmacological regulation of viral replication, using the rapamycin[76] or the Tet-On gene expression system[77,78] to regulate adenoviral E1A. This now opens the door to permanent external control of OVV during the treatment of patients. Various genetically engineered OVV and viruses with inherent oncolytic properties have recently been explored as anti-cancer agents, among them adenovirus[9,79,80], HSV[81-83], retroviruses[84], vaccinia virus[41], autonomous rodent parvovirus[85], vesicular stomatitis virus[86], Newcastle virus[87], and reoviruses[88-89]. Of these, HSV and adenovirus are the most widely studied ones. ONYX-015 was the first tested oAdV and is to date the most commonly used oAdV in clinical trials. Deletion of the adenoviral E1B-55kD enables the replication of ONYX-015 in cells with a defective p53 pathway and minimizes its replication in cells with a functionally active p53 pathway[9]. Thus, ONYX-015 is unable to replicate in normal cells, but strongly replicates in cancer cells. Several clinical trials have demonstrated the efficacy of ONYX-015 in patients with cancer. Strongest anti-tumor responses were observed in patients with squamous cell cancer of the head and neck[90,91], but responses to hepatocellular carcinoma[92], hepatobiliary tumors[93], and advanced pancreatic cancer[94] were reported, whereas no response was observed in patients with advanced ovarian cancer[95]. Two phase I/II clinical trials have provided evidence for the efficacy of ONYX-015 in metastatic gastrointestinal cancer[96,97]. Reid *et al*[96] administered ONYX-015 by hepatic artery infusion combined with 5-fluorouracil and leucoverin in 27 patients with both primary gastrointestinal carcinoma and liver metastases. The treatment was well tolerated showing only mild or moderate flu-like symptoms, including fever, myalgia, astenia and/or chills. Virus replication was demonstrated and three partial responses, four minor responses and nine stable diseases were documented as therapeutic outcome. In another study, patients with advanced sarcomas, among them patients with gastrointestinal stromal tumors, were given an intratumoral injection of ONYX-015 combined with MAP chemotherapy. The treatment was well tolerated and there was no significant toxicity. One of the six patients treated showed a partial response with an approximately 70% reduction of tumor size, and in four patients the disease stabilized[97]. Other oncolytic viruses like HSV, Newcastle virus and vaccinia virus also demonstrated their viro-oncolytic efficacy in clinical trials with cancer patients[41,98,99]. On the other hand, the studies revealed therapeutic limitations of the currently available OVV. Often, only a minority of patients shows a response, which is only partial and transient in most of the cases[5,97]. Obviously, there are several major limitations to the therapeutic potential of OVV. The key problems are low infectivity, replication rate and cytolytic activity of OVV.

To overcome these limitations, measures have therefore been taken to further develop OVV. The low transduction efficiency of oAdV due to low coxsackie-adenovirus receptor (CAR) expression can be enhanced by modifying the fiber proteins. This can be achieved by adding foreign peptides to the HI loop or the C-terminus of the fiber knob[100,101] or by substituting fibers of adenoviral 2 and 5 with fibers derived from other adenoviruses, which bind to receptor molecules other than CAR[102,103]. These strategies seem to be promising for the treatment of gastric cancer as well, since gastric cancer cells express low amounts of CAR, making it resistant to adenoviral infection[100]. Recently published data demonstrate that oAdV with RGD motif in the HI-loop of the fiber-knob region or replacing its adenovirus type 5 knob by an adenovirus type 3 knob has a stronger anti-tumor effect than unmodified oAdV in a gastric cancer model *in vivo*[100]. Another study investigated re-targeting a doubly-ablated adenovector to the epithelial cell adhesion molecule (EpCAM) by introducing a bi-specific single-chain antibody to EpCAM. EpCAM is highly expressed in gastric cancer but not in gastric epithelium. Consequently, the vector was highly selective for primary gastric tumors, while transduction of normal gastric epithelium and liver was low[104].

Another way to improve the efficacy of OVV is combining OVV treatment with conventional and other gene therapeutic strategies. Preclinical and clinical data demonstrate that OVV-induced tumor cell killing can be strongly enhanced by the expression of therapeutic transgenes from OVV like anti-angiogenetic factors, suicide genes, or tumor suppressor genes and simultaneous treatment with conventional chemo- and radiotherapy[43,96,105-110].

## PROSPECTS

Gene therapy has become a generally accepted new therapeutic tool in the treatment of cancer. More and more cancer patients profit from its use due to the progress made in the development of vector systems and gene therapeutic strategies. Thus, cancer gene therapy will increase its importance as a therapeutic tool even though many problems still need to be solved. One of the most important issues affecting the possible clinical application of gene therapy is the need to ensure the highest possible safety levels. Many clinical investigations have demonstrated that the currently available vector systems are well tolerated and side effects are acceptable. However, the use of retroviral vectors is discussed controversially, since 3 of 11 children with X-linked severe combined immunodeficiency, who were treated with a retrovirus, developed uncontrolled T-lymphocyte proliferation in a French gene therapy trial.

The major problem of cancer gene therapy that still remains is the relatively poor therapeutic outcome. This problem is not restricted to a specific tumor entity, but is rather a general problem. There may be many reasons for this, but it is widely agreed that this is mainly due to the relative resistance of cancer cells to introduce foreign material combined with low transgene expression *in vivo*. Thus, improved vector systems and application protocols will continue to be the biggest issues to be dealt with in cancer gene therapy in the next few years. However, important progress to overcome these limitations has already been made by the development of OVVs and vectors with increased tumor cell tropism.

Great progress has also been made in the development of gene therapeutic strategies in gastric cancer. New vector systems as well as the evaluation of new target genes and gene therapeutic strategies have substantially improved the chances for successful treatment of gastric cancer by gene therapy. The next challenge will be to test the results gained thus far in clinical studies.

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