Prostate Cancer Gene Therapy- What Have We Learned and Where Are We Going?

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With recent advances in genetic engineering, tumor biology, and immunology, gene therapy has been recognized as a promising new treatment option for various cancers, including prostate cancer. Several clinical trials of prostate cancer gene therapy, using therapeutic genes which include suicide genes, immunomodulatory genes, tumor suppressor genes, and anti-oncogenes, are under way and preliminary reports have emerged. Although gene therapy for prostate cancer is still at an early stage and requires additional technological breakthroughs, new insights obtained from recent clinical trials indicate a promising potential for prostate cancer gene therapy. In this report, general concepts, current progress, and future prospects in prostate cancer gene therapy are summarized. [Rev Urol. *2001;3(4):179–186*]

Key words: Prostate cancer • Gene therapy • Immunomodulatory genes • Suicide genes • Viral vectors • Oncogenes

In spite of significant advances in the treatment of cancer in recent decades, many malignancies remain resistant to current treatment modalities such as surgery, chemotherapy, radiation therapy, and immunotherapy. Prostate cancer is no exception.

Prostate cancer is one of the leading causes of cancer deaths in the Western world.[1] Current therapies are of limited efficacy in advanced disease. Recent advances in our understanding of the molecular biology of cancer and gene engineering have made gene-based cancer therapy an attractive tool. In 1990, the first human gene therapy was performed by Culver and associates[1,2] for a patient with severe combined immunodeficiency caused by adenosine deaminase deficiency. Since then, over 300 gene therapy protocols have been performed or are ongoing. Prostate cancer gene therapy protocols are also under way worldwide with some promising results.[2,3] In the earliest stages of development, overanticipation and fatal side effects due to gene therapy caused some appre-

hension about the clinical application of gene therapy. Nevertheless, reverse translation of early clinical data back to basic laboratory research led the field of human gene therapy to a new beginning. In this review article, general concepts of prostate cancer gene therapy are summarized,[4-6] information on current progress in this field is updated,[7,8] and future prospects of gene therapy are discussed.

Vehicles for Gene Delivery

The development of an efficient, safe, and reliable gene delivery system is one of the critical steps for gene therapy. Many pathways can be applied to deliver therapeutic genes to target cells or tissues. Each vector system has advantages and disadvantages and a certain application mode. Table 1 summarizes various characteristics and applications of human gene therapy pathways.

Retroviral vectorhead. The retroviral genome consists of three encoding regions responsible for viral replication:

1. the gag region, encoding group-specific antigens and proteins
2. the pol region, encoding reverse transcriptase
3. the env region, encoding viral envelope protein

These regions are flanked on either side by a long terminal repeat (LTR) region. Reconstruction of the retrovirus to a replication-deficient vector involves the replacement of viral genome with a therapeutic gene, measuring approximately 10 kb or less.

Adenoviral vector. The adenovirus consists of a long, double-stranded DNA genome (35 kb). Reconstruction of the virus consists of creating an expression cassette consisting of a promoter (Pro) and the desired therapeutic gene. The expression cassette is then inserted into the genomic E1a region, which normally encodes early proteins involved in rescuing cells from quiescence and allows rapid viral DNA and protein synthesis. Deletion of the E1a region renders the adenovirus replication deficient. The adenovirus binds to the host cell surface receptors, thus allowing cell entry. Viral capsid proteins are shed, leaving the episomal genome. The viral genome utilizes host transcriptional machinery to produce its therapeutic product. The viral gene product then carries out its local therapeutic effect.

Adeno-associated virus. The adeno-associated virus is a small linear single-stranded virus consisting of two genomic regions: 1) the rep region, encoding proteins involved in replication and integration; and 2) the cap region, encoding viral structural proteins. These regions are flanked on either side by a terminal repeat (TR). Reconstruction of the virus requires replacement of the rep-cap sequence with an expression cassette carrying promoter (Pro) and therapeutic gene. Replication of the wild-type virus requires cotransfection of the host cell with replicating adenovirus.

Classification of Prostate Cancer Gene Therapy

Gene therapy for treatment of cancer is generally substratified into four strategies based on the molecular target of gene transfer:

1. tumor suppressor gene therapy
2. suicide gene therapy
3. immunomodulatory gene therapy
4. antioncogene therapy

(see Table 2). In addition, oncolytic virus therapy using replication competent virus is also classified as a part of gene therapy. In this section, general concepts of each strategy are summarized with specific reference to prostate cancer. Clinical studies of prostate cancer gene therapy registered to the U.S. Recombinant DNA Advisory Committee (RAC) are listed in Table 3.

Tumor suppressor gene therapy. The tumor suppressor gene therapies that have been investigated in prostate cancer include p53, RB (retinobla-toma), and p21.[9,10] Experimentally, the introduction of normal

Table 1
Characteristics of Vectors for Gene Therapy

	Retrovirus	Adenovirus	Adeno-associated virus	Liposome
Advantages	Stable integration Large insert capacity Biology well investigated	High virus titer Highly efficient transfer Targets nondividing cells	Integrates into chromosome 19 Targets nondividing cells	Less immunogenic
Disadvantages	Low titer Infects only dividing cells	Host immune response Transient expression	Biology not well known Small insert capacity	Low efficient transfer
Application	Ex vivo strategy Initially well used	Direct injection Ex vivo transfer	Direct injection	Direct injection

(wild-type) p53 into prostate cancer in vitro and in vivo suppresses malignant phenotype and growth.[11] In spite of theoretical validity, there are two limitations to further clinical application. Not all prostate cancers express p53 gene abnormality, and transfection of all tumor cells with p53 gene is required in order to obtain complete tumor regression.

Suicide gene therapy. Suicide genes encode enzymes that convert nontoxic prodrugs into toxic metabolites that are lethal to the cells. Most of these enzymes originally come from bacteria, fungi, and viruses. Once a suicide gene is introduced into the targeting mammalian cells, an enzyme is expressed. After the systemic administration of the designated prodrug, the expressed enzyme, which is foreign to the cell, converts the prodrug into toxic metabolites, resulting in cell death.

The herpes simplex thymidine kinase (HSV-tk) gene is classically described as a model of the tumor "suicide gene."[12] Gene transfer of a drug-susceptible gene like HSV-tk renders target cells sensitive to subsequent drug (ganciclovir: GCV)-mediated cytotoxicity. The viral thymidine kinase gene is directed into human tumor cells by a gene vector. Transfected cells then produce intracellular HSV-tk capable of converting systemically introduced GCV to a phosphorylated product (GCV-P-P-P). The product, capable of blocking host cell DNA synthesis, accumulates intracellularly, causing ultimate cell death. One of the potential advantages of a suicide gene therapy using HSV-tk plus GCV is that it has "bystander effect."[13] When a cell dies as a result of gene therapy, it also exerts a lethal influence on surrounding cells, in part by the transfer of the toxic analogue via gap junctions or apoptotic vesicles.

Table 2
Cancer Gene Therapy: Strategies

1. Tumor suppressor gene therapy
Reversal of malignant phenotype by introducing normal tumor suppressor gene
p53, Rb (retinoblastoma), p21

2. Suicide gene therapy
Activation of prodrug in transfected cells
herpes simplex thymidine kinase (HSV-tk) plus ganciclovir (GCV)
cytosine deaminase plus 5-fluorocytosine (5-FC)

3. Immunomodulatory gene therapy
Induction and enhancement of tumor-specific immune response
ex vivo (tumor vaccine)
in vivo

4. Anti-oncogene therapy
Antisense oligonucleotides strategy to downregulate gene expression
c-myc, ras

5. Oncolytic virus therapy
adenovirus (CN-706, ONYX-015)
herpes simplex virus (G-207)
retrovirus

Immunomodulatory gene therapy. *Ex vivo tumor vaccine.* Ex vivo tumor vaccine strategy is the most widely and extensively evaluated immunomodulatory gene therapy strategy. Its goal is to induce or enhance a host antitumor immune response via the manipulation of tumor cells or immune cells. Generation of antitumor immunity, especially cell-mediated immunity (induction of tumor-specific cytotoxic T lymphocytes: CTL) is a multistep phenomenon, and many kinds of cytokines and molecules are involved. Among those cytokines, interleukin-2 (IL-2), IL-12, and granulocyte-macrophage colony-stimulating factor (GM-CSF) are potent and well-evaluated.[14,15]

The gene-modified tumor vaccine strategy of cancer therapy involves removing the primary tumor, which carries the entire spectrum of tumor antigens. A cell suspension consisting of tumor cells is created, and cells are transfected with a gene vector that encodes the cytokine or costimulatory molecules which are capable of creating antitumoral immunity. The transfected cell pool is then expanded, irradiated, and returned to the patient. The advantages of this strategy are that infecting all tumor cells is not mandatory, and systemic response indicates the treatment of the existing tumor and prevention of recurrence after definitive therapy such as radical prostatectomy. But a significant disadvantage of this strategy with respect to prostate cancer is the requirement of sufficient tumor tissue and successful cell culture.

In vivo immunomodulatory gene therapy. In vivo immunomodulatory gene therapy includes the direct tumoral or peritumoral injection of a gene vector that encodes a cytokine which is capable of inducing tumor-specific immune response. This is a form of in vivo tumor vaccine that overcomes the disadvantages of ex vivo gene therapy (the requirement of sufficient tumor tissue and successful cell culture).

Anti-oncogene therapy. Oncogenes have been identified in prostate can-

cer and serve as a target for gene manipulation. An antisense oligonucleotides strategy is applied to this form of gene therapy. Antisense oligo-nucleotides are synthetic nucleotides which are complementary to a specific RNA sequence and can inhibit the expression of functional gene products (oncogenes), resulting in growth suppression.[16]

Oncolytic virus therapy (replication-competent virus). Oncolytic virus is a genetically engineered or mutated virus that can replicate within the tumor cell after delivery and then lyse infected cells. Although this strategy is not gene therapy within the meaning of targeted gene transfer, it is sometimes classified as a part of gene therapy.

ONYX-015 is a genetically modified adenovirus that efficiently replicates in and kills tumor cells deficient in p53 tumor suppressor activity ("p53-deficient"cells) and not in normal cells.[17] The specific modification of the virus prevents it from replicating efficiently in normal cells.

Genetically engineered adenovirus (CN706), which replicates selectively in PSA-producing cells, can destroy cancer cells.[18] Enhancer/promoter constructs derived from the human prostate-specific enhancer (PSA) gene were inserted into adenovirus DNA so as to drive the E1A gene, which is an essential sequence for virus replication, thereby creating a prostate-specific enhancer-containing virus CN706. E1A was expressed at high levels in CN706-infected human PSA-producing LNCaP cells, and CN706 destroyed large LNCaP tumors and abolished PSA production in nu/nu mouse xenograft models with a single intratumoral injection. This form of gene therapy is applicable to advanced prostate cancer.

G207 is a multimutated herpes simplex virus 1 vector that lacks both copies of the ICP34.5 gene and contains an insertion of the *lacZ* gene inactivating the ICP6 gene.[19] G207 can replicate within cancer

Table 3
NIH-Approved Clinical Trials for Prostate Cancer Gene Therapy
(as of March 2000)

Category	Strategy	Vector	Transgene	Principal investigator	Research Institute
Tumor suppressor gene	Direct injection	Adenovirus	p53	C.J. Logothetis	M.D. Anderson Cancer Center, TX
	Direct injection	Adenovirus	p53	A. Belldegrun	UCLA School of Medicine, CA
Suicide gene	Direct injection	Adenovirus	HSV-tk	P.T. Scardino	Baylor College of Medicine, TX
	Direct injection	Adenovirus	HSV-tk	D. Kadmon	Baylor College of Medicine, TX
	Direct injection	Adenovirus	HSV-tk	S.J. Hall	Mount Sinai Medical Center, NY
	Direct injection	Adenovirus	HSV-tk	T.A. Gardner	University of Virginia, VA
Immunomodulation	Vaccine	Retrovirus	IL-2	B. Gansbacher	Memorial Sloan Kettering, NY
(Ex vivo)	Vaccine (Auto)	Retrovirus	GM-CSF	J.W. Simon	Johns Hopkins Oncology Center, MD
	Vaccine	Liposome	IL-2	D. Paulson	Duke University Medical Center, NC
	Vaccine (Allo)	Retrovirus	GM-CSF	J.W. Simon	Johns Hopkins Oncology Center, MD
	I.V. dendritic cell	Naked RNA	PSA	J. Vieweg	Duke University Medical Center, NC
Immunomodulation	Intradermal injection	Vaccinia	PSA	A.P. Chen	National Naval Medical Center, MD
(In vivo)	Intradermal injection	Vaccinia	PSA	D.W. Kufe (Phase-1)	Dana-Farber Cancer Institute, MD
	Intradermal injection	Vaccinia	PSA	J.P. Eder (Phase-2)	Dana-Farber Cancer Institute, MD
	Intradermal injection	Vaccinia	MUC1-IL-2	R. Fiblin	UCLA School of Medicine, CA
	Intradermal injection	Vaccinia	PSA	M.G. Sanda	University of Michigan Urology, MI
	Direct injection	Liposome	IL-2	A. Belldegrun (Phase-2)	UCLA School of Medicine, CA
Anti-oncogene	Direct injection	Retrovirus	c-myc	M.S. Steiner	Vanderbilt University Medical, TN
Oncolytic virus therapy	Direct injection	Adeno (CN607)	none	J.W. Simon	Johns Hopkins Oncology Center, MD

cells, causing cell death, but replication is limited in normal cells.

What Have We Learned?

Basic and clinical research on prostate cancer gene therapy. In the last few years, our understanding of prostate cancer biology and genetic engineering technology has dramatically increased, and data from early clinical trials are now available. These integrated basic research and clinical research achievements provide insights into future directions for gene therapy of prostate cancer. In this section, the most recent and clinically important basic research outcomes are introduced, and results of clinical trials are updated and summarized.

Tumor suppressor gene therapy. Because a single application of this strategy has little impact on tumor regression clinically, combined use with a conventional treatment modality has been considered. Nielsen demonstrated the enhanced efficacy of adenomediated p53 gene therapy for prostate cancer when combined with paclitaxel.[20] This combination is recommended for clinical application.

Suicide gene therapy. Preclinical research concerning the strategy of combining HSV-tk and GCV has revealed promising data relevant to prostate cancer treatment.[21] The effect was synergistic with androgen withdrawal in a mouse model of androgen-responsive prostate cancer.[22] Combination with IL-12 gene therapy showed significant synergistic effects in the orthotopic mouse model.[23] Local injection of HSV-tk gene vector followed by systemic injection of GCV caused systemic effects showing the suppression of preestablished lung metastasis in the mouse prostate cancer model, indicating possible production of systemic antimetastatic activity following a single in situ treatment with ADV/HSV-tk plus GCV in this model system.[24] Although numerous investigators have also suggested a role for the immune system in both local and systemic effects resulting from HSV-tk treatment, the candidate effector cell or cells mediating these activities is unknown. Hall identified the presence of NK cells within adenovirus/HSV-tk and ganciclovir-treated tumors, which serve to mediate both local and systemic antitumor activities in this model.[25] This experimental evidence has implications for further clinical application of this form of therapy including primary or adjuvant therapy and combination therapy with conventional modalities.

The development of an efficient, safe, and reliable gene delivery system is one of the critical steps for gene therapy.

Fourteen clinical trials of suicide gene therapy for cancer using adenovirus-mediated (retrovirus system is not included) HSV-tk gene and GCV are registered to RAC as of March 2000.[26] For urogenital cancer, four protocols for prostate cancer are registered and under way, and the initial Baylor protocol has already been concluded.

Among the clinical trials which were initiated as preliminary phase 1 studies, the suicide gene therapy protocol conducted by Herman and Scardino is the first to demonstrate anticancer activities of gene therapy in patients with prostate cancer.[2] In brief, patients were enrolled who had a rising serum prostate-specific antigen (PSA) level and biopsy confirmation of local recurrence of prostate cancer without evidence of metastasis one or more years after definitive radiation therapy. Patients received intratumoral injection of adenovirus vector encoding HSV-tk under ultrasound guidance. Intravenous administration of ganciclovir was performed for 14 days. Eighteen patients were treated with an escalating dose, and three patients achieved significant reductions of PSA by 50% or more. No serious adverse events were documented. These early data showing efficacy led to further trials to evaluate the utility of this form of gene therapy as an alternative treatment for prostate cancer.

Two protocols conducted at Baylor College of Medicine and Mount Sinai Medical Center involved neoadjuvant therapy before radical prostatectomy. Another protocol, conducted at Virginia University, is enrolling men with bone metastasis and using osteocalcin promoter-driven HSV-tk gene therapy.[27]

In Japan, a suicide gene therapy protocol for prostate cancer is planned and under government review. Protocol design is similar to the one performed at Baylor College of Medicine except for the patient criteria. Locally advanced hormone-refractory prostate cancer patients without definitive distant metastasis will be enrolled in this study. Finally, a protocol for prostate cancer was approved in the Netherlands in May 2000. Table 4 outlines and compares these protocols.

Immunomodulatory gene therapy. A clinical trial using GM-CSF gene-transduced autologous prostate cancer vaccines following radical prostatectomy has been conducted by Simon and associates and has demonstrated clinical safety and activity.[28] Similar adjuvant therapy clinical trials are being conducted with allogeneic prostate cancer vaccines using GM-CSF gene-transduced and irradiated human prostate

cancer cell lines, PC-3, and LNCap. This allogeneic strategy is a potent alternative to overcome a disadvantage of autologous vaccine strategy. Although results are preliminary, clinical activity was observed for the patients with micrometastatic prostate cancer showing PSA failure after prostatectomy. In fifteen of twenty-one (71%) patients, PSA velocity or average slope decreased after vaccination compared to before vaccination. Interestingly, new patient-specific oligoclonal antibodies appeared; these antigens are expressed by LNCap, PC-3, and normal prostate epithelium, suggesting broken immunologic tolerance following GM-CSF vaccine. These results warrant further study to evaluate their validity, and clinical trials are under way.[3]

Preclinical murine studies have demonstrated that intratumoral delivery of an adenovirus expressing IL-2 can successfully eradicate preestablished malignancy and confer immune protection from rechallenge. Phase 1 human trials in melanoma and breast cancer support bioactivity of the virus and have demonstrated minimal toxicity. In order to explore the activity of IL-2 in prostate cancer, a Phase 1 trial was conducted by Trachtenberg and associates in patients with locally advanced disease.[29] This Phase 1 trial demonstrates that adenomediated IL-2 delivery into the prostate by transrectal injection can be safely accomplished with minimal toxicity. A CD8+, TH1, T-cell inflammatory response to injection is observed even one month after injection.

Belldegrun and associates[30] have initiated a clinical study using a vaccinia virus expressing MUC-1 and IL-2 genes (VV/MUC-1/IL-2) for patients with advanced and metastatic prostate cancer to determine the safety of a multiple-dose regimen and to correlate changes in systemic immune function with clinical PSA response. Therapeutic response to intramuscular VV/MUC-1/IL-2 vaccination includes PSA decline, increased NK activity, upregulated cytokine expression, augmented T-cell activation signals, generation of serum-derived PBL growth-enhancing factors, and MUC-1 directed cytotoxicity.

Interleukin-12 (IL-12) is also a potent cytokine which elicits antitumor effects that involve the recruitment of specific immune effector cells.[31] It was shown for the first time that a single intratumoral injection of an adenovirus expressing IL-12 resulted in suppression of tumor growth, enhanced survival, and systemic antitumoral effect.

Table 4
Comparison of Clinical Protocols of HSV-tk Suicide Gene Therapy for Prostate Cancer

	Baylor	Baylor	Mount Sinai	Virginia Univ.	Erasmus Univ. (NL)	Okayama Univ. (Japan)
Prinicipal Invest.	P.T. Scardino	D. Kadmon	S.J. Hall	T. Gardner	C.H. Bangma	H. Kumon
Objectives	Safety	Safety	Safety	Safety	Safety	Safety
	(Clinical effect)	Gene exp.	Gene exp.	Gene exp.	Gene exp.	Clinical effect
		Biological effect	Biological effect		Biological effect	
		Neo-adjuvant	Neo-adjuvant		Neo-adjuvant	
Criteria of pt						
Stage	C	B	B	D	B	C
prior Tx	Radiation	None	None	Endocrine	None	Endocrine
followed Tx	None	Rad. Prost.	Rad. Prost.	None	Rad. Prost.	None
age	no range	35-75	no range	no range	35-70	20-
Vector						
Kind	Adeno	Adeno	Adeno	Adeno	Adeno	Adeno
Promoter	RSV	RSV	RSV	Osteocalcin	RSV	RSV
Dose (PFU)	10^8-10^{11}	10^{10}	10^{10}-10^{12}	10^8-10^{10}	10^{10}	10^8-10^{11}
Injection site						
	Prostate	Prostate	Prostate	Bone, LN	Prostate	Prostate

NL, The Netherlands; RSV, Rous sarcoma virus; PFU, Plaque forming unit; Rad. Prost., Radical Prostatectomy; LN, Lymph node.

Oncolytic virus therapy. CN706, a PSA-selective, attenuated, replication-competent, oncolytic Ad5 vector, was evaluated for safety and antineoplastic activity in a dose escalation trial of CN706 delivered stereotactically via the transrectal ultrasound-guided transperineal route in patients with locally recurrent prostate cancer following radiation therapy. The Phase I study demonstrates that PSA-selective oncolytic adenoviral gene therapy can be safely administered by routine prostate brachytherapy technique with minimal toxicity. Preliminary results suggest in vivo tumoricidal action, with four cases out of nineteen showing more than 50% decline of PSA, and adenoviral-induced immune response in patients with locally recurrent prostate cancer treated with CN706.[32]

Safety and social aspects of gene therapy. Two disappointing events in the field of gene therapy have recently given rise to scrutiny of the development of gene therapy. First, the death of Jesse Gelsinger at the University of Pennsylvania after injection of adenovirus vector into the hepatic artery for correction of his ornithine transcarbamylase deficiency. Second, in Memphis, the false alarm, rapidly rebutted, of HIV/HCV contamination of an adenovirus vector used to prepare a tumor vaccine for advanced relapsed neuroblastoma patients. Some difficult lessons were derived from these events with regards to the safety and social aspects of gene therapy.[33,34] Tight adherence to federal regulations by gene therapists, including prompt reporting of adverse events, is strictly required. For appropriate understanding of genetics by the general public, educational activities and an explanation of the trial process will be required.

Where Are We Going?

Preclinical investigation and early clinical data have yielded a solid scientific foundation despite recent setbacks. Although multiple potential strategies have been developed, early clinical trials in prostate cancer gene therapy are still in the phase I/II stage of development. Novel preclinical and early clinical data should be considered optimistically, yet cautiously, as this field emerges from its infancy. Technical hurdles that have emerged for extensive preclinical and early clinical trials have been clarified. Hurdles to be overcome are discussed in this section, along with future prospects and future directions to pursue.

One major problem in gene transfer and expression is the limited delivery system.

Cell targeting. Specific cell targeting is a critical way to increase treatment efficacy and decrease adverse effects. Current gene transfer modalities using virus vectors are not specific methods for cell targeting. Prostatic-specific membrane antigen (PSMA) is a potent surface molecule for prostatic cell targeting. Bangma and associates[35] have created a retargeting adenovirus vector system using a PSMA antibody, which has shown favorable activity.

Efficient gene transfer and expression. One major problem in gene transfer and expression is the limited delivery system. Currently available suicide gene therapy modality is based on a local injection of adenovirus vector into the cancer lesion. Although systemic antitumoral effects are obtained after the intratumoral injection of HSV-tk gene and GCV administration in the mouse model system, these effects have not yet been demonstrated in humans. Systemic administration of the vector followed by specific transfection of the gene at the targeted lesion or specific expression at the targeted lesion is the ideal system. Development of these ideal systems is essential for the establishment of effective treatment for androgen-independent prostatic cancer with multiple bone metastases, a goal of urologists. Tissue- or organ-specific promoter-driven suicide gene therapy is one of the innovative modalities that may solve this problem. PSA promoter[36] or osteocalcin promoter[37]-driven HSV-tk adenovirus vector has been constructed and its validity was tested, resulting in the initiation of a clinical trial using the osteocalcin system at Virginia University.[27] The development of a systemically injectable vector system will be a major challenge in the near future.

Vector development. Development of a new vector design is crucial in order to overcome barriers such as efficient and specific gene transfer, control of expression, and reduced adverse immunological response to vector sequences.

Prostate Cancer Gene Therapy as Translational Research

Gene therapy is regarded as translational research from the bench to the bedside, and must go back to the bench after clinical data are obtained. The reverse translation of early clinical data back to basic laboratory research also suggests the direction of the field of human gene therapy as we enter the twenty-first century. In this early stage, urogenital organs are excellent and characteristic targets for the application and evaluation of gene therapy. The prostate is an ideal target because direct, intratumoral injection under ultrasonographic guidance is a simple and

effective way to deliver the genetic agent, and prostate-specific antigen (PSA) is an extremely sensitive marker for therapeutic effectiveness.

Conclusions

Concordant progress both in the basic research and gene therapy technology will make cancer gene therapy available for wide-scale practice in the future. Many technical difficulties have to be overcome before effective gene therapy can be achieved. Nevertheless, we already have sufficient evidence to suggest that gene therapy will revolutionize the practice of medicine with the enormous increase in functional genes characterized as a result of the Human Genome Project. Needless to say, professional discussion about safety, experimental design, clinical benefits, and informed consent, as well as broad public discussion and ethical analysis, is essential to a carefully considered approach toward successful gene therapy. We are now entering the next phase of exciting possibilities in molecular medicine. ■

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Main Points

- Gene therapy for cancer follows various strategies according to the molecule targeted for gene transfer.
- Tumor suppressor gene therapy may be useful in combination with conventional treatment modalities.
- Preclinical research with suicide gene therapy has had promising results.
- Results of immunomodulatory gene therapy trials warrant further research.
- Oncolytic virus therapy can be safely administered by routine prostate brachytherapy.