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REVIEWS

Gene Therapy for Cancer: *Is there Light at the End of the Tunnel?*

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Abstract | Gene therapy is a novel modality of treatment which is being explored as a treatment option. Majority of the ongoing gene therapy clinical trials are for cancer, a disease difficult to treat with the existing therapies. Hence newer modalities of treatment are emerging. In cancer gene therapy, a gene or DNA is introduced into the tumour cell which would induce the tumour cell to die either directly or indirectly. Although this therapy is still in an experimental stage, it has shown some promise and there are at least two drugs for cancer which have been approved in China—the only country to have approved gene therapy based drugs. The different strategies of tumour cell kill as well as the various methods of gene delivery will be discussed in the following sections. For any new drug or treatment to be accepted in the clinics, it has to undergo rigorous clinical trials and approval by regulatory bodies. For gene therapy, it is a long and arduous path from research in laboratories to the clinics.

1 Introduction

Gene therapy is a treatment of a different kind where a gene or nucleic acid is used as a drug. Here, either the defective gene is replaced with the healthy gene—as in case of monogenic disorders; or the gene is selected to destroy the cell directly or indirectly by enhancing the immune system—as in case of cancer. Although the concept of gene therapy is simple, and a large number of clinical trials have been carried out, it has taken more than two decades for commercialization of any gene therapy product. The first gene therapy trial was in 1990 for Severe Combined Immuno-Deficiency, where the defective Adenosine Deaminase gene was replaced with the healthy gene.[1,2] However, the promise of gene therapy came to an abrupt end with the death of Jesse Gelsinger in 1999, who died due to profound immune reaction to his adenoviral mediated gene therapy,[3] and a few cases of immergence of cancer due to retroviral insertional mutagenesis.[4,5] Researchers have now developed better vectors to deliver the therapeutic gene and data from the clinical trials have shown that the approach can be safe and effective. The first gene therapy to be commercialized anywhere in the world is Gendicine (adenoviral serotype 5 mediated delivery of a human *P53* gene) which was approved for head and neck cancer, followed by H101, the first oncolytic virus to be commercialized, both in China.[6] There are other gene therapy products in the pipeline, mainly for inherited diseases.[7,8]

1.1 *Vectors used for delivery of therapeutic gene*

In cancer gene therapy, therapeutic genes including functional normal tumor suppressor genes, inflammatory immune cytokine genes, RNAi and microRNAs are delivered to the tumor cell using a carrier or a vector. Delivery of the therapeutic gene is one of the most challenging aspects of gene therapy. Researchers all over the world have been working on creating a safe and efficient vector. Vectors can broadly be divided into two types—viral and non-viral. Viral vectors were used as vehicles for transferring therapeutic genes from the beginning of gene therapy clinical trials. A summary of gene therapy clinical trials worldwide (n = 1843) is available in Journal of Gene Medicine

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(www.wiley.co.uk/genmed/clinical). According to their updated chart on vectors used in the clinical trials worldwide, almost 70% of the ongoing trials use viral vectors with vectors based on adenovirus being 23.3% and on retrovirus being 19.7%. Non-viral vectors include mainly naked/plasmid DNA, liposomes, bacteria and transposons.

1.1.1 Retroviral and adenoviral vectors: Viral vectors are the most efficient vectors for gene delivery and have been used in numerous clinical trials. They have evolved over a period of time to usurp the host cellular machinery to their own advantage, transport genetic information efficiently and express the viral genes. Viruses are made non-pathogenic and replication incompetent by removing some of the genes from their genome and inserting the cDNA for the gene of interest in its place. Viruses are capable of infecting a wide variety of cells in vitro as well as in vivo. Two of the most commonly used viral vectors are based on retrovirus and adenovirus. Retroviral vectors use mouse Moloney Murine Leukemia virus as its backbone and have single stranded RNA as their genome. They are capable of transferring their genome only into dividing cells since they are incapable of crossing the intact nuclear membrane. Retroviral vectors gave promising results in preclinical gene therapy studies. However, although majority of the early gene therapy trials used retroviruses as vectors they failed in human clinical trials,[9] and adenoviruses became the most widely used vectors in clinical trials. Unlike retroviruses, adenoviruses have DNA as their genome and infect dividing as well as non-dividing cells. They do not integrate in the host genome and therefore, the transgene expression remains transient. Moreover, Retroviruses integrate in the host genome randomly and could bring about insertional mutagenesis resulting in activation of oncogenes, as was the case in 5 patients in a clinical trial.[4] Lentiviruses including HIV, which are also retroviruses, are more efficient since they can infect both dividing as well as non-dividing cells by forming a pre-integration complex that can enter through the nuclear pore.[10] Initially, due to safety concerns, only non-replicating viruses were used as vectors. However, after numerous gene therapy trials demonstrating poor transduction of the virus in vivo, replication-competent viral vectors or oncolytic viruses have emerged as the vectors of choice.[11,12] Such viruses are made to replicate selectively in cancer cells thereby killing the cells by virus-mediated cytolysis. The replicating viruses spread through the tumour mass to infect other cancer cells. H101, which is a E1B deleted, replication-competent adenovirus, is the first oncolytic virus for use in cancer gene therapy to be commercialized, in China.[6]

1.1.2 Non-viral vectors: Non-viral vectors are being explored as gene delivery vectors and appear promising since they are less immunogenic than viruses and easier to produce. Naked plasmid DNA has been administered by intramuscular injections or using gene guns. Other non-viral means of delivering genes are generally either through cationic lipids or cationic polymers that can form stable complexes with nucleic acids and bind electrostatically to anionic proteoglycans present on cell surfaces. They enter cells within membrane coated vesicles, and their escape from these lipid-coated endosomes depends on incorporation of fusogenic lipids or endosomolytic function within the complexes. Among the cationic polymers, polyethylenimine (PEI) is the most commonly used DNA plasmid transfection agent because of its high buffering capacity (pH range 5.0 to 7.5), which facilitates rupture of the endosome membranes via a "proton sponge" mechanism.[13] According to Huang, the rate limiting step with non-viral vectors is the passage of the gene from cytoplasm to nucleus.[14]

1.2 *Cancer—an ideal target for gene therapy*

Gene therapy was initially thought to be ideal for monogenic disorders with the hope that it would merely involve replacing the defective gene with the healthy gene. However, issues such as vector design, safety, long-term regulation of transgene, and targeted delivery of therapeutic gene were some of the major challenges which remain to be addressed. On the other hand, most of these limitations could be bypassed for cancer gene therapy. The recurring theme in cancer gene therapy is to kill or slow down growth of cancer cells. Various strategies can be used in cancer gene therapy.

Some of the gene therapy strategies to kill or slow down growth of cancer cells are as follows:

- Immunomodulation
- Prodrug activation
- Anti-sense/RNAi
- Induction of apoptosis

1.2.1 Immunomodulation: Immunity plays a crucial role in tumour destruction. It is a well established fact that cancer patients have a compromised immune system. Attempts have been

made to enhance the immunity of cancer patients so that the tumour can be eliminated. Various cytokine genes as well as cell surface co-stimulatory molecules have been used to enhance immune response in patients.[15] There are reports that immunotherapy based on the adoptive transfer of naturally occurring or gene-engineered T cells can mediate tumour regression in patients with metastatic cancer (for review see[16]). Tumour microenvironment is reported to be full of inflammatory cells and cytokines which promote cancer growth.[17] This can be reversed to create a tumor environment permissive for immune destruction. Johansson et al.[18] have demonstrated that IFNγ and TNFα, alone or in combination, can effectively alter the vascular bed and alleviate the immunosuppressive tumor environment, thus enhancing tumor cell kill. They engineered IFNγ and TNFα with a tumor vasculature-targeting peptide (RGR peptide).[18]

Another important aspect of immunotherapy is the discovery of cancer vaccines. Dendritic cells are the most efficient antigen-presenting cells which induce cytotoxic responses in T cells against tumour antigens. One of the first dendritic based vaccines is Sipuleucel-T (Provenge) (Sip-T) which is an autologous vaccine approved by US FDA for the treatment of men with asymptomatic or minimally symptomatic castrate-resistant metastatic prostate cancer.[19] Sip-T is the re-infusion of a patient's antigen presenting cells from leukapheresis after ex-vivo exposure to a chimeric protein of human GM-CSF and prostatic acid phosphatase (PAP, expressed in approximately 95% of prostate cancers). This product also serves as a proof of principle for targeted immunotherapy for others cancers with defined cell surface markers.[19] Dendritic cells—either genetically modified in vitro to carry immune-stimulatory molecules[20] or fused with tumour cells[21]—are also being tested.

1.2.2 Prodrug activation: Prodrug activation gene therapy strategy, also known as suicide gene therapy, is based on the premise that a therapeutic gene coding for an enzyme converts an inactive, non-toxic drug to an active toxic form. One of the most widely and successfully used strategies is the use of Herpes simplex Thymidine Kinase (HSV-Tk) gene and the prodrug Ganciclovir.[22] Ganciclovir is phosphorylated by the HSV-Tk and subsequently by the endogenous cellular enzyme and converted to its triphosphate form, which interferes with DNA synthesis and brings about tumour cell kill.[22] Since human thymidine kinase has a low affinity for GCV, very little toxicity is observed in cells not expressing HSVtk. Nevertheless, tumour cell kill is also seen to occur in neighbouring tumour cells which have not received the enzyme, by a phenomenon known as "Bystander effect" and is a crucial process in increasing tumour cytotoxicity.[23–25] Cell kill has been demonstrated by the use of this strategy, in many tumour types both in vitro and in vivo as well as in numerous clinical trials.[26–28] A large number of clinical trials mainly for brain tumour, prostate cancer, mesothelioma and gynaecologic cancers have been carried out. In all the trials using suicide gene therapy, a common observation was the induction of both local and systemic immune response including infiltration of T and B cells in the tumour and increase in systemic cytokine levels.[26,29] We have demonstrated in vitro as well as in vivo that HDAC inhibitors such as Valproic acid increase suicide gene therapy—mediated tumour cell kill using adenoviral vectors.[30] This has led to planning a Phase 1 clinical trial of *in vivo* gene therapy using Adenovirus carrying Herpes Simplex Virus Thymidine Kinase gene under RSV promoter (Ad-RSVtk), and Ganciclovir along with HDACi—Valproic Acid (VPA), for the treatment of oral cancers.

1.2.3 Anti-sense/RNAi: Cancer is a genetic disease and the genetic landscape of a tumour is fast becoming apparent, thanks to the advances in DNA sequencing technology as well as Bioinformatic approaches. Techniques such as exome sequencing have accelerated the discovery of gene mutations and modifier alleles implicated in cancer which serve as targets for drug discovery. In the last two decades, a number of small molecule inhibitors as well as monoclonal antibodies have come into the market which target specific mutations or over expressed genes in the tumour. However, this has not resulted in long term cure for cancer and many of the molecular targets are difficult to inhibit. RNA-based therapeutics is becoming more popular mainly as an adjuvant therapy for cancer. In one of the clinical trials, the investigators tested a combination of p53 antisense oligonucleotides with genotoxic drug to enhance the killing of cancer cells.[31] The authors conclude that combination of antisense against p53 along with chemotherapy could potentially have a role in the management of AML.

The dsRNA molecules can down regulate the expression of a target mRNA in a sequence-specific manner. RNAi-based drugs look appealing; however, several challenges related to delivery of RNAi in patients limit the use of RNAi in the clinic. Nanoparticles have been used in order to reduce immune-mediated responses to systemic

RNAi based therapy.[32,33] It is believed that further investigation of the mechanisms of RNAi-based therapies as well as development of nanoparticles for delivery will help overcome limitations in their use in clinics.

1.2.4 Induction of apoptosis: Tumour cells evade apoptosis to survive, and therefore strategies to induce apoptosis hold considerable promise in anticancer therapy. Although there are numerous strategies to induce apoptosis including inhibiting proapoptotic molecules such as BCL2, BCL-X(L), activating procaspases, IAPs, etc, and activating pro-survival pathways, the most commonly used molecule to induce apoptosis in clinical trials worldwide is tumour suppressor gene p53. The tumour suppressor gene TP53, also called the guardian of the genome, recognizes DNA damage and triggers apoptosis or senescence, thereby preventing genetic instability and cancer. The p53 signalling pathway is invariably inactivated in cancer cells. This has led to tremendous efforts to develop anticancer therapy based on p53. A large number of clinical trials using p53 have confirmed safety and efficacy, which further led to development of gene therapy products. The first ever gene therapy product to be marketed in the world—Ad-p53 (Gendicine), has since been approved by the Chinese government to be used in conjunction with radiation therapy in head and neck cancers and other solid tumours.[6,34]

2 From Bench to Bedside

After carrying out extensive basic research followed by preclinical research, the results have to be translated into the clinics as therapy. Before the therapy is ready for the market it has to go through a number of clinical trials and obtain approvals from Regulatory bodies (see flow diagram, Fig. 1). A phase I clinical trial protocol has to be written. Phase I trials are only for proving safety and toxicity of the clinical grade genes along with their delivery vehicles. This is the first and major hurdle to be crossed in taking the product from bench to the bedside. The cost involved in making clinical grade vector is prohibitive as it requires a Good Manufacturing Practice (GMP) facility. Further, making a transition from laboratory scale to clinical scale is often challenging. Recognizing this problem in the US the National Institutes of Health established the National Gene Vector Laboratories (NGVLs) in 1995 to provide centralized resources for the production and distribution of clinical-grade gene vectors. Three institution—Indiana University, Baylor College of Medicine, and City of Hope—housed NGVL

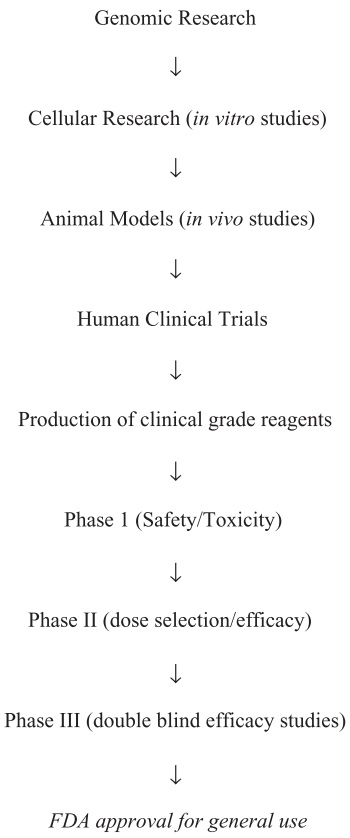

Figure 1: Path to gene therapy trials—from bench to bedside.

vector production facilities, each specializing in the development of different types of gene vectors. Two additional laboratories, located at the University of Florida in Gainesville and at the Southern Research Institute in Birmingham, Alabama, performed preclinical toxicology testing of vectors, a frequent prerequisite for human studies. In May 2008, National Gene Vector Biorepository (NGVB) was instituted. The goal of the NGVB is to provide gene therapy investigators with a variety of services that can enhance their research. However, this is an aspect of gene therapy which has been neglected and has received insufficient investment in all other countries.

Phase I clinical trial for cancer gene therapy is carried out in a small number of terminally ill cancer patients who have failed conventional therapy. Dose escalation can be a part of Phase I trial to find a safe dose in humans. Following successful completion of Phase I trial, a Phase II trial is carried out in a larger number of patients where efficacy of the therapy is assessed, following which a double blind, multi-centric Phase III trial is carried out. Most of the ongoing clinical trials worldwide are in Phase I/II with a few in Phase III and only 2 trials in Phase IV (Gene Therapy Clinical

Trials Worldwide, www.wiley.co.uk/genmed/clinical).

3 Success Stories in Gene Therapy

Although at a slow pace and with caution, significant progress has been made in the field of gene therapy and a lot has been learnt from human clinical trials worldwide. Close to 2000 clinical trials have been carried out worldwide. Some of the clinical trials have given promising results and provide hope for some of the untreatable diseases. Glybera (alipogene tiparvovec, an adeno-associated viral vector encoding human lipoprotein lipase gene) is in the news as it is likely to be the first gene therapy based drug to be cleared in the European Union.[8] Another promising therapy is for patients with inherited congenital blindness (Leber's congenital amaurosis, LMA) due to mutations in the *RPE65* gene. In patients with LMA, subretinal injections of adeno-associated viruses carrying a normal *RPE65* cDNA (AAV–RPE65) have been found to be safe and led to moderate improvement of retinal function in seven of nine patients, although the effect was much more pronounced in young children.[35] Gene therapy for some of the cancers have also given promising results in combination with either chemotherapy or radiotherapy.

4 Future of Gene Therapy

The progress in gene therapy has undoubtedly been slow. There have been many unavoidable and unexpected roadblocks which have delayed the progress of this novel therapy. One of the reasons for this has been the unavailability of good, clinical grade vectors for human trials in most academic institutes. The transition from laboratory scale to clinical grade scale had to be optimized and this did not receive enough attention initially. The French Biotechnology Institute Genethon is now all set to be the world's largest plant for producing and supplying large volumes of clinical grade viral vectors.[36] Genethon, along with NGVLs set up in the USA, will be a step closer for all academic scientists to make the transition from the laboratory to the clinics possible. To give a further boost to gene therapy, the American Society of Gene and Cell Therapy has sent the director of NIH, USA a list of the diseases (which includes two cancers) it believes will benefit most in the next 6 years from investment in translating basic research to the clinic.[36] With better gene delivery products and a better understanding of how the specific gene works in specific diseases, and with large scale production in place, we hope to see gene therapy finally becoming a reality.

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