GENETIC THERAPY: REPRESS, REPAIR OR REPLACE!

Until two decades ago, our genetic make-up was considered to be an entity that was entirely controlled by nature. Medical research is now on the threshold of manipulating this process to enable alteration of a defective gene responsible for life-threatening disease. Historically, biomedical research has seen a transition of quest through various stages. Starting with studies aimed at finding single gene–single function associations, the inquiries proceeded to genetic maps with a catalogue of genes, to a holistic gene complement catalogue for an organism to, finally, using the interrelationships of multiple genes and their functions to produce a molecular profile of an organism. This information has the potential to dramatically improve human health. The developments in the areas of classical gene therapy, functional inhibition using antisense molecules (such as antisense oligonucleotides or nucleic acids, ribozymes and aptamers), and gene-based rational drug designing taking place in pharmacogenomics can all be grouped together to form a novel medical discipline: genetic medicine, and the therapeutic aspects of these technologies together comprise genetic therapy.

Potentially, advances in genetic medicine could allow treatment of monogenic diseases by simply replacing or repressing the functioning of a defective gene. They could even address more complex polygenic diseases such as cancer, where multiple aberrant gene functions interact with environmental factors. In the latter case, one or more crucial genes in the cellular pathways such as proliferation, apoptosis, invasion, metastasis or angiogenesis can be targeted. There are six general levels of gene regulation in eukaryotes,¹ which are potentially amenable to gene therapy. These include transcriptional control, RNA processing control, RNA transport control, mRNA degradation control, translational control and protein activity control. In theory, any of these points of gene regulation, alone or in combination, can be targeted by genetic therapy.

Although they have exciting prospects, developments in the field of genetic medicine have many medical, ethical and socio- logical roadblocks that must be overcome before this modality can be accepted as a standard form of medical care. The issues in a series of monographs have many medical, ethical and socio- logical roadblocks that must be overcome before this modality can be accepted as a standard form of medical care. The issues in a series of monographs have,
are then re-introduced into the patients. This is the most popular format attempted for treatment of haematopoietic disorders. Alternatively, DNA can be delivered directly into the target tissue (in situ), e.g. into the lungs by aerosolic inhalation or into solid tumours by injection. The third and most common format is in vivo genetic therapy, by injection into the blood stream, following which the therapeutic DNA is expected to ‘home’ onto the target tissue via the circulation. Modified viral genomes have been the most preferred delivery vehicles since they deliver therapeutic DNA into target tissues with high efficiency. Six main groups of viruses are currently used: retroviruses, adenoviruses, adeno-associated viruses (AAV), lentiviruses, Herpes simplex viruses (HSV) and pox viruses.

Gene therapy strategies employing conditionally lethal ‘suicide’ genes and pro-drugs have engendered increasing interest in recent years. While numerous enzyme–pro-drug systems have been explored, the HSV-thymidine kinase (HSV-TK)–Ganciclovir (GCV) combination is the most studied. Exposure of HSV-TK expressing mononuclear cells to GCV results in apoptosis. Ganciclovir is a nucleoside analogue that is monophosphorylated by HSV-TK and further phosphorylated by human TK to GCV-triphosphate, which inhibits DNA synthesis and induces apoptosis. The TK gene is expressed in cells but is phenotypically silent when there is no GCV added. The TK gene thus acts as a ‘suicide trigger’ in the presence of GCV.

The drawbacks associated with the use of viral vectors, particularly those related to safety problems, have prompted investigators to develop alternative methods for gene delivery. The use of cationic lipid-based systems is one such approach. While non-viral vectors such as lipoplexes are easier to produce and have low immunogenicity, their gene transfer efficiency is much lower than that of viral vectors and the transgene expression is transient. Improvements in the features of lipoplexes aimed at facilitating their use in vivo (e.g. colloidal stability) is crucial to generate such viable alternatives to viral vectors.5

RIBOZYMES

Ribozymes catalyse site-specific cleavage or ligation of phosphodiester bonds in RNA or DNA. They are the tools of choice for silencing defective gene function in autosomal dominant genetic diseases, because introducing a normal gene will not work in such diseases. Thus, in cancers (caused by hyperactivation of oncogenes) or neurodegenerative diseases (caused by aggregation of mutant protein), ribozymes effectively reduce pathogenic gene expression by interfering with the angiogenesis pathway. Because of the rapid and extensive absorption after extravascular injections, either intraperitoneal (i.p.) or subcutaneous (s.c.) administration is considered to be optimal.5 In experiments with monkeys, angiuzyme seems to be well tolerated, with no drug-associated morbidity or mortality.6 Phase II clinical trials with angiuzyme are beginning for patients with metastatic breast cancer and metastatic colorectal cancer. Preliminary results demonstrate that angiuzyme is well tolerated, without significant side-effects.10

HER-2/neu is an oncogene that encodes the 185 kDa transmembrane tyrosine kinase receptor in the epidermal growth factor receptor (EGFR) family. This family of receptors has been shown to be over-expressed in several cancers, including head and neck, renal, bladder, ovarian, prostate, colon, breast, ovarian and non-small cell lung carcinoma. Herzyme is a ribozyme created to block HER-2/neu protein synthesis.

GENETIC THERAPY: WHERE ARE WE NOW?

Across the globe, there are a number of clinical trials under way. Clinically useful gene therapy trials must satisfy three essential prerequisites: (i) the genetic material must be delivered to target cells with high efficiency at low cost and acceptable side-effects; (ii) introduction of the extrinsic genetic material must not result in any undesirable genetic or non-genetic change; and (iii) the expression due to the extrinsic genetic material must be regulatable. Let us briefly go through the phases of typical clinical trials.

Clinical trials for genetic therapy

The clinical investigation of an untested genetic drug is divided into three phases. Although the phases are conducted sequentially, they may overlap. The three phases are:

Phase I: This includes the initial introduction of an investigational new drug into humans. These studies are usually conducted in healthy volunteer subjects and are designed to determine the metabolic and pharmacological actions of the drug in humans, the side-effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. Phase I studies also evaluate drug metabolism, structure–activity relationships and the mechanism of action in humans. The total number of subjects included in Phase I studies generally range between 20 and 80.

Phase II: It includes the early controlled clinical studies conducted to obtain some preliminary data on the effectiveness of the drug for a particular indication or indications in patients with the disease. This phase of testing also helps to determine the common short term side-effects and risks associated with the drug. Phase II studies usually involve several hundred people.

Phase III: These studies are intended to gather additional information about the effectiveness and safety that is needed to evaluate the overall benefit–risk relationship of the drug. Phase III

Ribozymes in hepatitis C infection

The hepatitis C virus (HCV) has infected over 100 million people worldwide. Hepatuzyme developed by Ribozyme Pharmaceuticals Inc. (RPI), USA, cleaves all known HCV genotypes, thus preventing viral replication. Phase I/II studies have demonstrated that the drug is safe and can be given as a daily at-home self-injection.

Ribozymes in cancer

Besides hepatuzyme for HCV, other hammerhead ribozymes developed by RPI are Angiuzyme and Herzyme. Both these were primarily developed against cancers.

Angiuzyme specifically cleaves mRNA for the vascular endothelial growth factor receptor-1 (VEGFR-1) (Flt-1), thereby selectively interfering with the angiogenesis pathway. Because of the rapid and extensive absorption after extravascular injections, either intraperitoneal (i.p.) or subcutaneous (s.c.) administration is considered to be optimal.5 In experiments with monkeys, angiuzyme seems to be well tolerated, with no drug-associated morbidity or mortality.6 Phase II clinical trials with angiuzyme are beginning for patients with metastatic breast cancer and metastatic colorectal cancer. Preliminary results demonstrate that angiuzyme is well tolerated, without significant side-effects.10
studies also provide an adequate basis for extrapolating the results to the general population and transmitting that information in the physician labelling. Phase III studies usually include several hundred to several thousand people.

Though the initial genetic therapy trials focused on monogenic diseases, currently, cancer tops the list, with the distribution being 62% for cancer, 13.3% for monogenic diseases, nearly 7% each for infectious and vascular diseases, and less than 2% for other diseases (http://www.wiley.co.uk/wileychi/genmed/clinical/). In cancer, the target genes include tumour suppressor genes, oncogenes, cytokine genes, histocompatibility antigen genes and suicide genes. As far as delivery vehicles are concerned, viruses still dominate, though alternative methods are also being pursued rigorously (Table I).

The majority of the clinical trials utilize autologous cells as sources. While various routes are being attempted for delivery, intratumoral injections or infusions are the most common (nearly 24%), followed by intravenous (18%), subcutaneous (11%), bone marrow transplantation (8%) and intramuscular (7%). Other routes include intradermal, intraperitoneal and intranasal deliveries. The diseases for which genetic therapy is currently undergoing clinical trials are listed in Table II.

The distribution of clinical trial protocols by phases is given in Fig. 1, while that by continents, diseases and genes targeted is given in Figs. 2, 3 and 4, respectively.

RESULTS OF SOME SELECTED CLINICAL TRIALS

Cancer
Currently, the majority of approved clinical trials of gene therapy involve cancer patients. Since it is not possible to replace or correct all wayward genes involved in the multistep carcinogenesis process, gene therapy strategies have focused on the replace-

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<th>Table I. Therapeutic gene delivery methods</th>
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<td>Chemical (lipofection)</td>
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<td>RNA (ribozymes)</td>
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<td>Plasmid/naked DNA</td>
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<td>Other (antisense)</td>
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<th>Table II. Diseases and genetic therapy: Ongoing clinical trials</th>
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<td>Cancer</td>
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<td>Ovarian</td>
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<td>Other diseases</td>
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Cystic fibrosis

Nearly 1000 mutations have been identified in the cystic fibrosis (CFTR) gene (http://www.genet.sickkids.on.ca/cftr/). Gene therapy

aims to deliver copies of the normal CFTR gene via aerosols to the airway epithelium using viral or non-viral vectors. Viral vectors include adenoviruses, AAV, or sendai viruses; non-viral vectors include cationic liposomes or cationic polymers. These advances have been recently reviewed by Doull. Both viral- and cationic liposome-delivered gene treatment in the nose can produce some gene transfer (as detected by the presence of CFTR mRNA) and some rectification of chloride transport. Since the observed changes are not close to values in subjects without cystic fibrosis, Doull is of the opinion that it is unlikely that any Phase III trials will start within the next 5 years.

Haemophilia

The current treatment of haemophilia, whether due to a deficiency of Factor VIII or Factor IX, consists of periodic replacement of the deficient factor with human blood products or recombinant proteins that have been synthesized in tissue culture. Continuous endogenous production of these factors can protect against bleeding and minimize exposure to infectious agents that may be present in replacement therapies. This goal is achievable with gene therapy. In vivo delivery of viral vectors that express the desired coagulant protein (via retrovirus vectors based on Moloney murine leukaemia virus, or via adenoviruses and AAV) is an approach that has been used in gene therapy trials so far. Roth et al. have recently described an alternative approach: transkaryotic gene therapy. They introduced the Factor VIII gene into skin fibroblasts ex vivo by electroporation and implanted a genetically modified clone of the cells into the patients' peritoneal cavity. Their results showed detectable levels of Factor VIII in 4 of 6 patients who received such cells, with 2 patients expressing therapeutic levels. The requirement of recombinant Factor VIII decreased in the 3 patients with the highest plasma levels of Factor VIII activity, and the number of episodes of spontaneous bleeding decreased substantially in all the patients. However, Factor VIII levels decreased and were undetectable 10 months after administration of the modified fibroblasts in most of the patients. This is the first demonstration of measurable levels of Factor VIII in plasma following gene therapy. While the therapy seems to be promising, the inability to retrieve engineered cells after intraperitoneal delivery could be problematic, since analysis of molecular mechanisms of decline of therapeutic expression cannot be studied.

Restenosis

Thickening of the arterial intima and smooth muscle cell proliferation are major problems after vascular surgery and other types of vascular manipulation. Restenosis denotes recurrent narrowing of blood vessels after successful revascularization procedures such as percutaneous transluminal angioplasty (PTA). Despite wide acceptance of PTA as the treatment of choice for atherosclerotic lesions, restenosis continues to be a difficult and expensive complication of the procedure. Data from experimental animal work indicate that gene therapy may modify intimal hyperplasia after arterial injury, but there are few clinical trials on restenosis in patients. Preliminary clinical results show only limited success in altering restenosis rates. Gene therapy for angiogenesis has been demonstrated to increase the formation of collaterals and functionally improve limb ischaemia. Another ongoing gene therapy clinical trial will test the efficacy of plasmid-based naked DNA transfer for the VGEF gene into arteries by percutaneous transfer to bring about neovascularization and reduced neointimal thickening.

Despite the enthusiasm generated by clinical trials worldwide,
the awareness of safety issues, pitfalls and limitations of genetic therapy cannot be overemphasized. The target tissue-specific delivery and temporally and spatially specific therapeutic gene expression still remain the major constraints. The first documented gene therapy-related death two years ago in the USA is one stinging reminder of this reality. Eighteen-year-old Jessie Gelsinger, who was being treated with adenovirus-mediated gene therapy, died in September 1999 following multorgan failure, and the postmortem showed that despite the expected tissue specificity of the viral vectors, numerous non-target organs were highly infected with the adenovirus.

Site-specific integration of the therapeutic gene is required to prevent inactivation of either the introduced gene or of the crucial endogenous tumour suppressor genes. Conversely, it is also desirable to avoid activation of endogenous oncogenes. In addition, regulated expression rather than a constant level of production of a therapeutic gene product is often a requirement. However, both site-specific introduction and temporal regulation of a therapeutic gene are at best only experimental at present. Since viral vectors pose challenges regarding safety risks and cost-efficient commercial production, non-viral vectors have been touted for some time now as ultimate alternatives. A number of these are in various stages of development, but are yet to deliver on their promise in clinics.

The field of genetic medicine is becoming a mammoth industry. Presently, there are 130 genetic therapy-related companies. Of these, 52 are involved in the development of viral vectors while 48 are developing non-viral vectors, including liposomes, naked DNA, artificial chromosomes and protozoan and bacterial vectors. Eighteen companies specialize in regulated or targeted gene delivery while 12 are involved in the production of genetic therapy devices (http://www.wiley.co.uk/wileychi/genmed/clinical/). The details of commercial therapeutic gene products will be described in the next review in this series, 'Nucleic acids in commerce'.

FUTURE DIRECTIONS IN TISSUE-SPECIFIC THERAPEUTIC GENE EXPRESSION AND DELIVERY TECHNOLOGIES

The issues leading to successful gene therapy include dealing with the efficiency of gene transfer, regulation of gene expression and avoidance of the potential risks associated with the use of viral vectors. Minimizing or excluding inappropriate gene expression in surrounding non-target cells is of great importance for numerous therapeutic gene approaches. The successful use of inducible and tissue-type specific promoters would allow targeted gene function with stable, long term gene expression. The technologies related to this attractive concept have been reviewed extensively by Walther and Stein.19

Hepatocyte-mediated gene delivery via gene transfer into isolated hepatocytes can be accomplished via non-viral or viral vectors. Extensive repopulation of the liver by transplanted hepatocytes is achievable by specific mitotic stimulation of the transplanted cells while simultaneously preventing proliferation of the host hepatocytes. While prior treatment with a plant alkaloid retrorsine or preparative irradiation of the liver can be used to prevent host hepatocyte proliferation, mitotic stimulation of the transplanted hepatocytes can be brought about by partial hepatectomy, expression of Fas ligand, or thyroid hormone administration. Hybrid viruses which combine the high transduction efficiency of adenoviral vectors and the integrative capacity of adenovector-associated vectors are being designed.20

Through years of dogged research, it has become increasingly evident that mitochondrial dysfunction contributes to a variety of human disorders, including neurodegenerative and neuromuscular diseases, obesity, diabetes, ischaemia–reperfusion injury and cancer.21 Of particular interest in cancer is the fact that mitochondria have also been recognized as the 'motor of cell death', reflecting their crucial role in the process of apoptosis. Development of cationic vesicles as a mitochondria-specific DNA delivery system has heralded a novel avenue for gene therapy.22 Kagawa et al. have recently reviewed developments in the field of mitochondrial gene therapy using cybrid formation and microinjection.23

Tschoep et al. have recently described the use of lithotripsy shock waves as a new physical method for the direct transport of antisense oligonucleotides into the cytoplasm and nucleus of cells.24 They found this method to be superior to electroporation for the cells (human peripheral blood mononuclear cells) tested.

WHERE ARE WE HEADED?

Chimeraplasty

Chimeraplasty or targeted gene correction is still in its infancy and faces many technical challenges. The pivotal molecule in the technology is a short stretch of nucleic acid that contains DNA interspersed with small amounts of RNA. The chimeric RNA–DNA structure seeks out and hybridizes with a specific target mutant gene sequence and triggers the cell's natural DNA repair machinery so as to 'repair' the defective endogenous sequence as dictated by the exogenous 'corrective sequence'. This approach may have advantages over virus-mediated gene therapy procedures for genetic disorders caused by an autosomal dominant mutation. In such disorders, where one flawed copy of a gene is sufficient to cause disease, adding a second normal copy to the cell may not be enough to overcome the effects of the mutation, and correcting the mutant allele may be more profitable. Thus, for example, scientists from Jefferson Medical College in Philadelphia, USA, could employ chimeraplasty to repair the tyrosinase gene mutation responsible for albinism in a strain of mice and restore the normal gene function, allowing formerly albino cells to produce melanin pigment.25 The technology does have potential limitations, though.26 The most crucial one pertains to possible 'bystander effect', whereby gene sequences closely homologous to the target gene may be accidentally affected. The human genome is replete with such families of structurally homologous genes, including those coding for structural as well as signalling protein molecules.

Molecular immunotherapy

One of the main objectives of cancer immunotherapy is the activation and increase in number of antitumour effector cells. Hence, genetically modified tumour cell vaccines have been proposed for elicitation of antitumour effector cells. Native α antigen (α Ag) of Mycobacteria, which cross-reacts among Mycobacteria species, may play an important biological role in host-pathogen interaction because it elicits various helper T-cell type 1 immune responses.

Cutaneous gene therapy

The skin is the most accessible somatic tissue. Aside from inherited skin diseases such as epidermolysis bullosa (EB) and ichthyosis, physiological and pathological processes such as wound healing, cancers, genetic diseases, baldness and various systemic metabolic disorders are under investigation as potential candidate diseases for cutaneous gene transfer.

The genetic basis for many skin diseases has been dissected
extensively. Thus, mutations in the CK4 and CK14 genes are responsible for EB simplex (characterized by a split in the dermal-epidermal junction), and mutations in the genes encoding the α3, β3 and γ2 chains of laminin 5, or the two subunits of the α4 β1 integrin and the bullous pemphigoid antigen cause junctional EB (marked by cleavage in the basal lamina). In the dystrophic forms of EB, the anchoring fibrils undergo cleavage and this is shown to be due to mutations in the type VII collagen gene. All these genes form potential gene therapy targets, and clinical trials are under way for many of these.

Spinal cord injury

Using ex vivo gene therapy, specific cell types for gene therapy and neural repair can be targeted, such as Schwann cells, fibroblasts, glial or stem cells. Neurotrophins are known to enhance extension of specific populations of injured axons. Cells selected in vitro for successful incorporation of the neurotrophin transgene can be analysed for transgene expression and biological activity. Cells with high transgene expression are expanded in culture and grafted into the host spinal cord. There is no risk of immunological rejection because cells from the same individual are used. Thus, this approach has the capability of providing a high concentration of long term, localized growth factor delivery to a site of injury. However, gene therapy has not yet achieved the goal of diversifying axonal growth after initial axonal growth, although such methods are under development.

Cancer

K-ras mutations occur frequently in non-small cell lung, colorectal and pancreatic carcinomas; H-ras mutations are common in bladder, kidney and thyroid carcinomas; N-ras mutations are found in melanoma, hepatocellular carcinoma and haematological malignancies. The ras signalling pathway has therefore attracted considerable attention as a target for anticancer gene therapy, just as interrupting the ras signalling pathway has been a major focus of new drug development efforts. The major therapeutic approaches include the inhibition of ras protein expression (through ribozymes, antisense oligonucleotides or antisense RNAs) or inhibition of downstream effectors of ras function. Blocking a downstream target such as MAP-ERK-Kinase (MEK) may abrogate a number of different signalling pathways. Such inhibition may permit targeting of a broad range of tumours but increases the potential of toxic effects. On the other hand, blocking an upstream target such as EGF receptor (HER-1) is likely to limit the range of tumours that can be treated to only those that aberrantly express this receptor, but conversely, reduce the potential for toxicity. Ongoing clinical trials will resolve the issue as to which of the two approaches is superior.

Although most thyroid cancers are cured by surgery and radiotherapy, death occurs in as many as 20% of patients with advanced differentiated and anaplastic tumours. To date, chemotherapy has been relatively ineffective for these patients. Gene therapy could be an alternative approach. Thyroid tumours are an especially good target, because genes expressed in the tumours such as thyroglobulin, thyroid stimulating hormone (TSH) receptor and calcitonin have no or very limited expression elsewhere. Besides, even if destruction of all normal thyroid tissue were to occur as a result of gene therapy, it would be inconsequential since thyroid tissue can be regenerated, as opposed to liver or lung. Direct CT-guided needle injection into a tumour, demonstrated to be useful for the treatment of non-small cell lung cancer by Kauczor et al., could be applicable for gene therapy in thyroid cancer.

AIDS

The magnitude of the HIV epidemic worldwide and limitations of the existing treatment modalities demand continuous development of novel treatment strategies. Gene therapy approaches that target viral replication have received substantial attention. These and various other approaches have recently been reviewed by Buchsacher and Wong-Staal.

Pain management

Noceception is the term commonly used to refer to the perception of pain. The receptors involved in pain detection are referred to as nociceptors—receptors for noxious stimuli. These nociceptors are free nerve endings that terminate just below the skin and detect cutaneous pain. They are also located in tendons and joints. Treatment of chronic pain, especially of neuropathic aetiology, is rather difficult and resistant to many available pharmacological therapies. Current analgesic agents may be limited with regard to analgesic efficacy or side-effects. Gene therapy for the management of pain has become a conceivable reality through advances in our understanding of the neurobiology of noceception and knowledge of the fundamental genetic structure of many nociceptive targets. The gene overexpression strategy for gene therapy in pain management could potentially target antinociceptive targets such as the acetylcholine, cannabinoid, opioid, and serotonin receptors (defective gene function replacement strategy). Another strategy already active in clinical trials is an antisense oligonucleotide-mediated knockdown of target protein levels presumably through enhanced mRNA degradation (i.e. defective gene function repression strategy). This knockdown strategy targets disease-causing or potential pronociceptive targets, such as N-methyl-D-aspartate receptors (NMDA), PKC and neurokinin 1 receptors. Tools for such gene therapy have been extensively reviewed by Wu et al. recently. Another review by these same authors details the potential targets. Thus, tachykinin NK1 receptor, PKC γ-isoform, vanilloid receptors, cannabinoid receptors, acetylcholine receptors and NMDA subtypes of glutamate receptors could serve as very useful gene therapy targets.

Hypertension control

Hypertension is a complex pathophysiological state that leads to serious complications which include heart failure, coronary artery disease, valvular heart disease, cardiac arrhythmia, cardiomyopathy and abnormal renal function. Traditional therapies, while effective, offer no long term cure and often have lower effectiveness due to patient non-compliance. Through advances in the molecular understanding of processes that underlie hypertension, namely, hormonal, metabolic and genetic factors, an alternative approach such as gene therapy is likely to provide long term control over hypertension. Thus, since the inhibition of angiotensin II (Ang II) formation through the angiotensin-converting enzyme (ACE) inhibitors or actions of Ang II (AT1 receptor antagonists) have shown to be effective in treating a majority of human hypertension cases, retrovirus-mediated delivery of the AT1 receptor-antisense can be used to prevent hypertension and related cardiovascular pathophysiology.

SUMMARY

Human diseases have been dissected at the molecular level, and most have been found to have their bases in genetic malfunctioning. Following the age-old principle of "set a thief to catch a thief", nucleic acids have been awarded the role of rectifying these genetic defects. Through intensive research, nucleic acids have
begun to earn their rightful place as therapeutic tools, as adjuncts to traditional therapies or as definitive therapies on their own. The commercial potential of these developments in the rapidly expanding global economy is also immense. However, careful consideration of the appropriate target cells, delivery vectors, timing and dosage is essential. The ethical and social impact of the technology must also be taken into account.

Besides genetic therapy (delivering ‘corrective’ nucleic acid sequences into the target cells), genetic medicine will have two major auxiliary impacts on human health. First, the nucleic acid sequences will increasingly provide ‘tracking devices’ for disease progression in response to therapy, thus serving as an adjunct to other therapeutic modalities such as radiotherapy, chemotherapy and immunotherapy. Second, the same technologies that are being developed to ‘vector’ the nucleic acid sequences into the target cells will become methods of delivery into these cells for novel drug molecules, which themselves will be products of genetic medicine.

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