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Comments and Critique

Gene Therapy for Cancer

WE NOW know that cancer is a disorder of somatic cell genetics resulting in a clone of cells with an abnormal pattern of growth control. Over the last few years we have learnt much about some of the genes involved in oncogenesis. Oncogenes and tumour suppressor genes are clearly part of the normal human genome—vital in the transduction of physiological signals from the outside of a cell to its nucleus [1]. The subversion of this apparatus by a variety of mechanisms can cause cancer. At the moment the picture is confusing. The precise molecular pathogenesis of even a single type of cancer is not yet understood. Almost certainly a sequence of events is necessary for a tumour to emerge [2].

Unfortunately, so far, our new knowledge has had little impact on treatment. It is true that interesting prognostic factors such as the increased expression of N-*myc* in neuroblastoma [3] and of c-*erb*B2 in breast cancer [4] have been identified, but novel therapeutic approaches have not yet been successful. There are now several encouraging *in vitro* observations which suggest therapeutic possibilities at a genetic level. Firstly, interference with the production of mutant p21 *ras* protein in transfected cells causes reversion to a benign phenotype [5]. Secondly, replacing inactive tumour suppressor genes in cells known to bear inactivating mutations causes reversion of some retinoblastoma, osteoblastoma and prostate cancer cell lines [6]. But is it realistic to carry out genetic manipulation *in vivo*?

There are many technical stumbling blocks to be overcome but possibilities for the gene therapy of cancer are beginning to emerge. Indeed, the first clinical experiment has already been performed, and its long-term results are eagerly awaited. This involved the insertion of an active tumour necrosis factor (TNF) gene into tumour-infiltrating lymphoctyes from a patient with melanoma. Whilst TNF produces dramatic responses in animal tumours, clinical trials with recombinant drug administered intravenously have produced disappointing results. The discrepancies between animal and clinical data are probably explicable by an almost 40-fold increase in toxicity of the drug in humans compared to rodents. By using TNF-expressing lymphocytes as a vectoring system, high local concentrations of the cytokine can be achieved. This type of system could rapidly be adapted for the targeting of other recombinant cytokines, growth factor antagonists, toxin–ligand conjugates or even monoclonal antibodies and their single chain antigen-binding protein derivatives. As well as providing novel delivery systems, gene insertion can be used to determine the mechanisms behind cellular cytotoxicity by allowing activated cells to be tracked for long periods of time [7].

Such systems all rely heavily on selective tumour infiltration by appropriately manipulated cells of the immune system. But few tumours can be targeted in this way. A more sophisticated gene therapy system involves the insertion of deleterious genes into vectors which can only be expressed in the tumour or cells of the same tissue of origin when not essential to the body as a whole. Carcinoembryonic antigen, alpha-fetoprotein (AFP), amylase, calcitonin and prostate-specific antigen provide examples of such proteins. Retroviral shuttle vectors containing the relevant tumour or tissue specific promoter linked to a toxic product can be constructed in such a way as to only be expressed when inserted into cells which have the necessary transcription factors. An interesting model system exists for hepatoma. Retroviral vectors in which the AFP promoter has been coupled to viral thymidine kinase lead to high levels of this enzyme only in hepatoma cells. There are certain nucleoside analogues which are potent cytotoxics when activated by thymidine kinase. This approach has been called virally directed enzyme prodrug therapy (VDEPT). By using the targeted activation of prodrugs it may be possible to provide the necessary selectivity to effect

Table 1. Gene therapy for cancer treatment

Use of genetically engineered antitumour drugs	
Recombinant cytokines	
Growth factor antagonists	
Humanised monoclonal antibodies	
Toxin–antibody immunoconjugates	
Toxin–ligand conjugates	
Single-chain antigen binding proteins (SCABP)	
Down-regulation of specific gene expression using informational drugs	
mRNA	Antisense oligonucleotides
mRNA	Specific ribozymes
DNA	Oligonucleotides–triplex DNA formation
RNA polymerase	Oligonucleotides
Transcription factors	Oligonucleotides
Protein	Specific proteases
Gene replacement for mutant oncogenes/tumour suppressor genes	
Homologous recombination (new for old)	
Excision	
Introduce a specific block to gene function	
Gene addition	
To produce aberrant product with new function	
To protect bone marrow by CSF expression	
To protect bone marrow by MDR1 expression	
To introduce tumour suppressor genes	
To produce new cytostatic product within the tumour	
Virally directed enzyme prodrug therapy (VDEPT)	
To produce active cytokine within the tumour	
TNF in TIL cells	

CSF = colony-stimulating factor, MDR = multidrug resistance and TIL = tumour-infiltrating lymphocyte.

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tumour destruction. The elimination of all cells of a particular lineage, whether normal or malignant, could also be a goal. Thus genetic pancreatectomy and bilateral mastectomies might in future be possible as non-invasive procedures.

Another method to manipulate the somatic genetics of cancer *in vivo* is to down-regulate the expression of specific genes using informational drugs. These can act at several levels. Antisense oligonucleotides can block the activation of transcription by binding to promoter regions, and of translation by preventing transport of mRNA to the ribosome. Furthermore, the recent demonstration that oligonucleotides can recognise DNA sequences specifically resulting in a triplex DNA cofiguration which sterically hinders gene expression provides another avenue for gene therapy. Specific ribozymes and proteases could also lead to the effective down-regulation of tumorigenic proteins.

Finally it may be possible to replace defective tumour suppressor genes known to be relevant in a wide range of human cancers. Homologous recombination—the exchange of new genes for old—can work well *in vitro*, but can it be made to work in the complex environment of a bulky and perhaps poorly accessible tumour within a patient? It is more likely that such approaches will be most powerful in the adjuvant setting, relying on surgery, radiotherapy and in some cases chemotherapy to reduce tumour burden as much as possible. Other strategies include increasing the resistance of normal bone marrow cells to high-dose chemotherapy by enhancing their expression of colony stimulating factors or multidrug exporting proteins such as P glycoprotein. Whether this can enhance survival without the risks of an autologous bone marrow transplant remains to be seen.

The ethics of gene therapy for cancer are relatively straightforward despite the endless debate about other potential uses. No attempt is being made to change the germ line so the fear of mutant monsters emerging can be discounted. Perhaps the biggest worry is that of raising our patients' expectations prematurely. The real question is when will the technology, which at the moment does not even work well in tissue culture, be ready for clinical exploitation. Table 1 lists some of the possibilities. It is likely that by the end of decade the human genome will have been completely sequenced giving us a superb database. New flexible vectors will be available for *in vivo* use. We will have a much clearer understanding of the mechanics behind the interaction of DNA, RNA and protein during the control processes of transcription. All this could provide the momentum on which to base novel therapeutic strategies for the next millenium.

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1. Sikora K, Evan G, Watson JV, eds. *The Cancer Cell. Br Med Bull* 1991, **47**, Edinburgh, Churchill Livingstone.
2. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. *Cell* 1990, **61**, 759–760.
3. Kemshead JT, Patel K. N-*myc* its place as a diagnostic and prognostic indicator in neuroblastoma. In: Carney D, Sikora K eds. *Genes and Cancer*. Chichester, Wiley, 1990.
4. Gullick WJ. The role of EGFR and the c-*erb*B2 protein in breast cancer. *Int J Cancer* 1990 (Suppl. 5), 55–61.
5. Mukhopadhyay T, Tainsky M, Cavender AC, Roth J. Specific inhibition of K-*ras* expression and tumorigenicity of lung cancer cells by antisense RNA. *Cancer Res* 1991, **51**, 1744–1748.
6. Bookstein R, Shew JY, Chen PL, Scully P, Lee WH. Suppression of tumorigenicity of human prostate carcinoma cells by replacing mutated Rb gene. *Science* 1990, **247**, 712–715.
7. Rosenberg SA, Aebersold P, Cornetta P, *et al.* Gene transfer into humans—immunotherapy using tumour infiltrating lymphocytes modified by retroviral gene transduction. *N Engl J Med* 1990, **323**, 570–578.

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Are We Giving Tamoxifen for Too Long?

THE DEVELOPMENT of anti-oestrogens [1, 2] and the ubiquitous use of tamoxifen to treat selected patients at each stage of breast cancer [3] has provided the practising oncologist with an agent that appears to be safe and effective. However, issues of safety and continuing efficacy need to be addressed and debated so that our concepts and perceptions of an agent can be revised in the light of current clinical experience.

The concept of adjuvant therapy provided the opportunity to cure patients with breast cancer by destroying the micrometastases that were disseminated throughout the body. Naturally, adjuvant cytotoxic chemotherapy was initially selected as the appropriate strategy because of proven efficacy in advanced disease; however, concerns about an unacceptable level of side-effects often resulted in the delivery of suboptimal doses of drugs. In contrast, tamoxifen therapy was known to have a low level of side-effects and some women with advanced disease had been found to receive palliative benefit for about a year. As a result many trials [4, 7] evaluated the benefit of 1 year of adjuvant tamoxifen therapy. This decision was made because tamoxifen could not be expected, based on experience in advanced disease, to provide benefit for the majority if used longer. Indeed the prolonged use of tamoxifen could have lead to premature drug resistance. Nevertheless, laboratory studies [8] were able to provide a rationale to attempt trials of long-term (2–5 years) tamoxifen therapy [9–13]. Although unselected patients, i.e. receptor negative or unknown patients, were entered in the studies, an improvement in disease-free survival and, in fact, survival was eventually observed. This result contrasts with the disappointing performance of 1 year of adjuvant tamoxifen therapy in individual trials to improve survival.

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