

Editorials

Gene therapy for cystic fibrosis: what message for the recipient?

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The notion that genetic diseases might be cured by correcting or replacing the abnormal gene in the affected tissues is an attractive one, and probably reflects the average educated layman's concept of gene therapy. In the case of severe combined immunodeficiency due to adenosine deaminase deficiency, such curative gene therapy has in fact been achieved by correction of autologous bone marrow cells *ex vivo* before returning the marrow stem cells to the patient. There are understandable professional and public fears about gene therapy which might introduce additional "corrected" genes into the germ tissue of individuals and thereby potentially into the permanent human gene pool, and for that reason germ line gene therapy is regarded as unethical throughout the world. The limitation which this places on the treatment of a multi-system disease whose clinical effects begin in fetal life is therefore obvious, and expectations of a cure for cystic fibrosis by gene therapy are intrinsically unrealistic.

An alternative strategy is to look for control, rather than cure, of a disease such as cystic fibrosis by repeated delivery of the normal gene to the target tissue for as long as the patient lives. This is the approach which has been taken by teams on both sides of the Atlantic, and an update on progress is given in the paper by Middleton and Alton in this issue of *Thorax*.¹ The intention of using the gene as therapy is to "normalise" the electrolyte transport in airway cells, and to correct other associated functional disorders, thereby preventing cystic fibrosis-associated lung disease. As the authors point out, there are formidable problems, not least because we do not yet have an ideal vector (the Postman) nor do we know with certainty the specific cell type to which the message needs to be delivered (the Box). The expectations of the research programmes are three-fold: (1) the system will work—that is, the mail will be delivered; (2) the package will be worth receiving—that is, the intention of therapy will be realised; and/or (3) even if the first two expectations are not met, we will learn something useful about the function of CFTR and about gene therapy in general.

Some of the problems which have been encountered were predictable—and predicted. Early American studies used the adenovirus as a vector but it is both pathogenic and antigenic. It is therefore unsuitable for repeated use, and we still do not know how frequently repeated doses of the gene will be required to maintain an adequate level of function. Can viruses be modified to make them more innocuous—that is, more like a liposome—and, if so, would they then be less effective? Liposomes as vectors, on the other hand, are relatively inefficient and although clear functional results can be demonstrated after direct

application of liposome-wrapped genes to the nasal airway, it would seem likely that uptake will be less efficient when an aerosolised liposome preparation is directed at airways whose epithelium is damaged and heavily coated with purulent mucus, as in cystic fibrosis. Could we devise intravenous vectors which would home in on the target cells in the lungs, supposing we knew with rather more certainty than we currently possess whether the delivery box is the ciliated bronchial epithelium or cells in the submucosal glands? Could the wild-type CFTR gene be delivered to other organs such as the liver and pancreas using different vectors? In most cases, of course, this would not prevent the destructive process in the pancreas which in most cases is well established before birth, but it might perhaps avert diabetes. Similarly, such treatment, even if given at birth, would be too late to save the *vas deferens*.

Gene therapy is not the only way in which the lung disease of cystic fibrosis might be controlled. For example, aerosolised amiloride and uridine triphosphate have shown promise in pilot studies.² Recent clinical observations have suggested that drugs used for cancer chemotherapy may induce multidrug resistance proteins which are very similar to CFTR, and which may provide an alternative chloride channel.³ The observation that reducing the temperature of cystic fibrosis fibroblasts in culture enhanced glycosylation of CFTR and its insertion into the cell membrane argued that, at least for the most common mutation ($\Delta F508$), the processing of mutant CFTR might be similarly enhanced by bringing about a chemical, rather than a physical, change in the cells by means of an appropriate pharmacological agent.⁴ Other therapeutic agents being evaluated include sodium 4-phenylbutyrate (a transcriptional regulator), the xanthine CPX, phosphodiesterase inhibitors such as milrinone, and the tyrosine kinase inhibitor genistein. Updates on progress were given in numerous papers and posters at the North American Cystic Fibrosis Conference in October 1997.⁵ My personal view is that one or more of these pharmacological agents may reach the market considerably before gene therapy.

Demonstration of physiological efficacy is a long step from demonstrating improved well being and prolonged survival. If and when gene therapy is shown to "normalise" the chloride secretory response across the bronchial mucosa for a reasonable length of time, and to continue to be effective on repeated administration, meaningful trials could begin. The initial phases of such trials would include monitoring for side effects and evaluation of clinical efficacy. Indeed, it is difficult to evaluate new forms of treatment without randomised controlled trials. Because gene therapy will, of necessity, first be tried in patients who

already have lung disease, what degree of clinical improvement would we accept as a satisfactory end point? How much would life have to be prolonged to justify imposing a further treatment modality on these long suffering patients? The history of cystic fibrosis is littered with treatments which were fashionable for a while, believed by most clinicians to be effective, but when submitted to rigorous analysis were rightly discarded, thereby often reducing the therapeutic burden for the affected person.

I make no apology for coming back to the patient. Cystic fibrosis patients are, in many cases, unrealistically pinning their hopes upon gene therapy which, as was pointed out in an editorial in the *Lancet*, may have been "oversold" to research funding bodies and to the general public.⁶ For the foreseeable future their prognosis depends more upon the less glamorous development of current methods, and perhaps new pharmacological approaches, than upon gene

therapy. The here and now message (the Fax?) is that delivery of gene therapy cannot be guaranteed.

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- 1 Middleton PG, Alton EFWF. Gene therapy for cystic fibrosis: which post-man, which box? *Thorax* 1998;**53**:197-9.
- 2 Knowles MR, Oliviera KN, Hohneker KW, *et al.* Pharmacologic treatment of ion transport in the airway epithelium in cystic fibrosis. *Chest* 1995;**107**:71-6S.
- 3 Lallemant JY, Stoven V, Annereau JP, *et al.* Induction by antitumoral drugs of proteins that functionally complement CFTR: a novel therapy for cystic fibrosis? *Lancet* 1997;**350**:711-2.
- 4 Denning GM, Anderson MP, Amara JF, *et al.* Processing of mutant cystic fibrosis transmembrane conductance regulator is temperature-sensitive. *Nature* 1992;**358**:761-4.
- 5 North American Cystic Fibrosis Conference, Nashville, October 1997. *Pediatr Pulmonol* 1997;Suppl 14:1-352.
- 6 Editorial. Supervising gene therapy, openly. *Lancet* 1997;**350**:79.