Commentary
Gene therapy for arthritis – where do we stand?
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Abstract
The successful use of biologicals in the treatment of rheumatoid arthritis, psoriatic arthritis and spondyloarthritis has had a major impact on the management of these conditions. The challenge in the development of gene therapy as an alternative to these current treatments is to demonstrate that such therapy is more advantageous for patients from the therapeutic and safety points of view. Also, it will need to be demonstrated that gene therapy for the arthritides is economically feasible and that patient populations worldwide will be able to access these treatments.

Introduction
Gene therapy for arthritis has been the subject of several recent reviews [1-5], in which the targets, vectors and methods of delivery are well documented. Interestingly, many of the titles of these reviews contain a question mark, as does the present commentary. This is because, in contrast to other areas of medical research in which gene therapy is proposed, in the arthritides biological therapy is already having great impact and some of the side effects can be prevented. This poses great challenges to gene therapists involved in this area.

Current biological therapies in arthritis and their limitations
It has been proposed that complete remission of early rheumatoid arthritis may be possible with anti-tumour necrosis factor (TNF) therapy [6,7]. However, uncertainties persist regarding whether diagnosis is accurate at this early stage of disease; furthermore, access to facilities for early detection and availability of expensive anti-TNF treatment are still limited by lack of government funds. Differences in funding available for anti-TNF therapy in countries of the western world are dramatic (IMS Market Research, September 2004 unpublished, and G Panayi, personal communication), and in the UK only part of the population has access. With the increased use of anti-TNF therapy in other clinical conditions [8], pressure to provide access will have important economic implications. However, it is likely that, with the availability of additional biologicals, market forces may help to reduce prices.

Surprisingly, different anti-TNF drugs have different therapeutic properties [8]. This is partly due to the effector properties of their Fc portion, the different pharmacokinetics of the agents (resulting from different routes of delivery), and the immunogenicity of each particular compound, which in turn depends on each patient’s immune repertoire.

State of gene therapy in arthritis
A recent search of the PubMed database revealed that during the past 14 years we have seen an increase in the number of papers published related to gene therapy and arthritis. This activity peaked in 2000–2001, with 132 publications, decreasing to 85 in the period 2003–2004. These numbers are small when compared with the numbers of publications on gene therapy in cancer or cardiovascular disease, which have been relatively stable since the year 2000 at about 2100 and 500 papers per year, respectively. This difference in publication numbers reflects both the urgent need for alternative treatments and the different ethical issues raised in the treatment of fatal diseases such as cancer and cardiovascular disease in comparison with nonfatal diseases such as arthritis.

Does this mean that research into gene therapy for arthritis is in decline? The answer is probably ‘no’. Gene transfer is also an important tool with which to elucidate the pathogenesis of disease and to probe new potential molecular interventions.

The current success with biologicals, the fact that patients will not enrol in new clinical trials unless they have failed to respond to biological therapies, and the serious adverse events reported in certain trials of virus-mediated gene therapy are helping to focus the minds of gene therapists. Despite the above factors, phase I clinical trials in arthritis

TNF = tumour necrosis factor.
using both \textit{in vivo} and \textit{ex vivo} gene therapy approaches have been conducted \cite{9} and some are ongoing \cite{3}.

\textbf{The way forward}

All of the successful biological therapies mentioned above are expensive and must be administered to the individual for the rest of their life. Cessation of treatment is normally accompanied by disease relapse. Most of these biologicals are cytokine inhibitors based on immunoglobulin backbones. Thus, they exert their effects by inhibiting the actions of cytokines, and their pharmacokinetics are relatively similar.

Some questions remain to be answered. For example, will delivery of anti-inflammatory cytokine production as well as initiate repair and signalling cascades be more effective than cytokine inhibitors? Could cytokine delivery be engineered to be targeted and more effective? Can cytokine therapy accelerate the repair process, thereby shortening the duration of administration and thus reducing costs? These questions will be difficult to address using protein therapy because the half-life of cytokines is shorter than that of immunoglobulin-based molecules, and they have pleiotropic effects due to receptor expression in many tissues. Systemic delivery of cytokines has several limitations, although these can be overcome by targeting their activation to sites of disease through protein engineering to generate latent cytokines \cite{10,11} or by building immunocytokines \cite{12,13}.

Gene delivery is an important tool that may help to address the limitations of cytokine therapy mentioned above and permit local cytokine delivery in a safe and effective manner, as has already been demonstrated in many studies conducted in animal models of arthritis. Local production and local consumption of cytokines can be achieved by engineering autologous cells that target the joints or by direct delivery. The proposed use of stem cells for cartilage repair will necessitate genetic engineering, at least for local immune suppression \cite{14,15}.

\textbf{Planning a safe clinical trial in arthritis}

As we pointed out previously \cite{1,4}, safety is of prime concern when treating a nonfatal chronic disease such as rheumatoid arthritis. Any delivery system should be nonimmunogenic. Hence, of the available viral vectors, both retrovirus and adeno-associated virus could be considered, as well as naked DNA. The hydrodynamic delivery of naked DNA to muscle and liver has revealed a new important paradigm to achieve nonviral, long-term gene expression \cite{16,17} that seems amenable to scaling up for human intervention.

The limited clinical experience to date with use of constitutive promoters that express cytokine inhibitors has not yet shown any safety issues. However, because of the relapsing and remitting phases of disease, use of transcriptionally regulated vectors to achieve cytokine expression will be extremely important \cite{18}, adding another layer of safety to gene therapy.

Local delivery could be advantageous, and the major efforts have been in this direction. Elegant studies using retrovirally transduced lymphocytes, as carriers of therapeutic genes, have been conducted in animal models \cite{19-21}. However, this approach needs further research if we are to unravel the changes that occur in these lymphocytes and to develop the capacity to switch off gene expression or destroy the lymphocytes in case of an adverse event. The use of autologous synoviocytes expressing interleukin-1 receptor antagonist has been the main thrust of the phase I clinical trials to date \cite{3,9}. Whether this approach will be therapeutic and cost-effective is not yet clear.

Direct delivery of adeno-associated virus constitutively expressing a TNF receptor–immunoglobulin fusion protein to the joint is already underway, but this vector may not permit tight transcriptional regulation because it can only package a restricted amount of genetic information \cite{22}. Whether this delivery system will be safe in the long term remains to be assessed.

It is our view that systemic hydrodynamic delivery of plasmid DNA appears to be the most feasible and efficient procedure, and should be further investigated. It will be important at first to determine whether the technology is capable of delivering similar levels of anti-TNF in the blood as are measured in the clinical trials with infliximab or etanercept, because the toxicology, immunogenicity and pharmacodynamics of the anti-TNF compounds are well established. Using transcriptional control will be of utmost importance, as explained above. If this approach is safe and successful in achieving clinical benefit in the long term, a second phase of clinical studies could be developed using combinations of anti-TNF therapy with methotrexate, or using latent cytokines and their combination with cartilage anabolic factors to facilitate rapid repair of damaged joint tissue.

\textbf{Conclusion}

The future for gene therapy in rheumatoid arthritis seems clearer and more defined, thanks to many new developments in gene transfer, gene regulation and drug design.

\textbf{Competing interests}

The author is founder of Stealthyx Therapeutics Ltd, which develops latent cytokines and other peptide-based therapeutics.

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