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Editorial

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Targeting 'horror autotoxicus' by gene therapy: results, challenges and the future

Our sophisticated immune system evolved to protect us against exogenous pathogenic organisms and combat disease, and therefore necessitates the ability to differentiate between 'self' and 'nonself'. While the immune system is normally tolerized to autoantigens, 'horror autotoxicus' (a term coined by Paul Ehrlich at the turn of the last century) or the attack of 'self' by the immune system can occur, resulting in autoimmune disease.

Autoimmune diseases are multifactorial, polygenic diseases of unknown aetiology. Self tolerance can be broken by many stimuli including infectious pathogens that mimic self-antigens in genetically susceptible individuals. An excellent example of a well-characterized, environmentally triggered, human autoimmune disease is coeliac disease where the protein gliadin found in gluten induces inflammation of the gut. Its mechanisms of pathogenesis serve as a paradigm for autoimmunity (see review by Londei *et al*).

Current treatment strategies primarily aim either to immunosuppress (reducing inflammation in a general or more antigen-specific manner) or to reinstate tolerance. Autoimmune disorders have been found to have in common the dysregulation of cytokine networks. Many of the reviews in this edition have therefore concentrated on the manipulation of cytokines as therapeutic targets in autoimmune disease. Local cytokine networks are also affected in other conditions and gene therapy research in autoimmunity may also have an impact for future therapeutic interventions in other areas of medicine such as organ transplantation and cardiovascular disease. However, cytokines have pleiotropic functions and their biological effects will depend on many variables such as the presence of a specific receptor on the cell surface, the type of tissue/cell responding, its stage of differentiation, as well as how it integrates the myriad other stimuli triggered by other cytokines, adhesion molecules, cells and extracellular matrix components during the pathological process. Cytokines can be involved in the survival of cells in the damaged tissue, as well as the regulation of the immune response to autoantigens driving the pathogenic process locally and systemically. These issues pose both technical and biological challenges.

Despite these complexities, it appears that targeting proinflammatory cytokines, such as tumour necrosis factor (TNF) or IL-12 via cytokine inhibitors or using anti-inflammatory cytokines such as IL-4 and IL-10, show impressive therapeutic benefit in most animal models of human autoimmune disease (see reviews by Baker and Hankey, Wirtz and Neurath, Mageed and Prud'homme, Bottino *et al*, t'Hart *et al*). However, certain therapeutic genes have quite different biological activities when delivered systemically than when delivered locally (see review by Robbins *et al*). These issues will have to be taken into consideration for future clinical trials.

Therapeutic genes can be delivered locally by injecting vectors directly *in vivo* to the affected organ or *ex vivo* by engineering immobile cells (eg myocytes, fibroblasts and synoviocytes) and mobile cells of the immune system (eg dendritic cells, T and B cells and macrophages) which may be tissue or antigen-specific or be engineered to be so.

Autoimmune diseases include at least 5% of diseases prevailing in the Western World. They are of high economic impact as they last the lifetime of the individual and most successful therapies currently available slow disease progression, but do not repair the damage caused by the immune system.

Some autoimmune diseases have high morbidity in severe cases (eg Crohn's disease, rheumatoid arthritis, type I diabetes and multiple sclerosis), some declare onset at an early age (eg multiple sclerosis and systemic lupus erythematosus) and many progress through cycles of remission and relapses. Hence, any gene therapy intervention considered will need to be long term, tightly regulated and safe (see review by Gould and Favorov).

Clinical trials in gene therapy have been almost exclusively focused upon life-threatening conditions, but with potential clinical applications today reaching to fields such as autoimmunity, this brings ethical issues into view that were hitherto unfaced. With potential benefits clearly overwhelming the risks for most clinical trial participants with terminal conditions, especially

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where conventional treatment had failed, clinical trials have been given ethical approval. But what about research participants with nonfatal, chronic, variable, conditions with conventional treatment options? Although it can be argued that such conditions are degenerative and disabling, result in considerable reduction in quality of life and at present poorly treated, when would it be ethical for researchers to test gene therapy in such clinical settings?

While ethical committees, patient information and consent procedures are designed to protect and ensure that individuals are fully aware of what they are participating in, we must ask ourselves whether this truly is in the patient's interest. Risks thought until only recently to be only theoretical, such as insertional oncogenesis, have been found to be a reality (whether as a direct result of gene therapy or as an unfortunate side effect) and the result to the individual and their family could be devastating.

Risk taking is part of the advancement of medicine. Many advances in medicine with huge present-day benefits such as transplantation have a chequered history of failures and development takes a number of decades to minimize risks. If the precautionary principle was strictly adhered to, medical advances would be few and far between.

Gene therapy research has undoubtedly yielded a huge body of knowledge and insight to the pathological and physiological processes underpinning a wide range of conditions. From these review articles, it is clear that gene therapy has the promise to alleviate suffering in autoimmunity. Researchers are facing the question of when and how to translate basic science to widespread testing in humans. Are we really yet sure that the risk to individuals is sufficiently minimized in nonlife-threatening conditions such as arthritis to justify to take this step? As in all clinical research, the best interest of the patients must always be primary.

It is imperative that patients and carers are not given unrealistic expectations about the potential of this technology. Balancing the potential with the reality (particularly the timeframe in which we can expect to see widespread effective use of gene therapy) is a notoriously difficult issue.

Since pathology is accompanied by degeneration, strategies to deliver a regenerative process alongside gene therapy should be sought. Gene therapy alone may halt the disease process, but for regeneration, great potential lies with the use of stem cells. Much interest has been generated in the potential of stem cells, derived either from embryonic, foetal or from adult sources, to repair degenerative diseases.

Ethical issues over the use of stem cells, particularly embryonic stem cells, place researchers in a difficult position. Embryonic stem cells hold potential for unlimited, 'made to order' cells and tissues for vital organs. Prolife organizations have been outspoken about the use of such tissue, along with the use of foetally derived stem cells, and advocate the use of adult stem cells, which do not compromise the sanctity of life (see review by Jorgensen *et al*). Countries differ in permitting research into human embryonic stem cell. For example, in the UK and Australia, embryonic stem cell lines can be created from spare embryos, but in many countries this is not permitted.

While stem cells hold promise, and are already delivering results in regenerative medicine, the science of engineering stem cells is in its infancy. Engineered stem cells have a large therapeutic potential not only for repair of adult tissues, but also have the capacity to deliver therapeutic molecules to target organs.

Of particular interest are mesenchymal stem cells, which are pluripotential and are particularly accessible and therefore offer opportunity for *ex vivo* genetic manipulation. Progress in identifying factors that drive differentiation of such stem cells *in vitro*, as well as their pluripotential nature *in vivo*, make these cells ideal candidates for engineering for therapeutic purposes without the ethical issues that accompany the use of embryonic or foetal cells.

These reviews show how much we have improved our understanding of the pathogenesis of autoimmune diseases, with target molecules better defined, and new ones being discovered. New therapeutic interventions will be tried, each posing technical, scientific and ethical problems. It will be important to address not only immunomodulation but also tissue regeneration. Hence, combined therapies will probably be more effective than single-molecule-based therapies. The challenge continues….

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