The management of rheumatoid arthritis (RA) presents a major challenge to the medical community. The physical and psychological sequelae of this chronic inflammatory arthropathy not only diminish the quality of life, but also reduce life expectancy. Furthermore, the high prevalence of the disease, combined with the costs associated with treatment, disability and loss of productivity, raise substantive socio-economic issues.

As the pathoetiology of the disease remains unknown, therapy, of necessity, is symptomatic and mainly addresses pain and disability while attempting to slow the progress of the disease. Conventional therapies, including corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs) and slow-acting anti-rheumatic drugs (SAARDs), have been established, in part, empirically and, in part, in response to the apparently autoimmune features of RA. In general, conventional pharmacotherapy has yielded disappointing results and the side-effects may even contribute to the higher mortality of patients with RA compared to the general population.

In the past few years, efforts have been made to formulate new therapeutic concepts based on the growing understanding of the pathophysiology of RA, which is summarized in the following. RA is a chronic, systemic, inflammatory disease that leads to progressive destruction of the joints. Histopathologically, the affected joints are characterized by a highly hyperplastic synovium that is infiltrated with inflammatory cells such as monocytes, and lymphocytes, the latter often concentrated within follicle-like aggregates. Infiltration of the synovium occurs through multiple blood vessels created through the process of neoangiogenesis. These newly created blood vessels have been found to express specific adhesion molecules on the endothelium that guide inflammatory cells to the site of inflammation and enhance their transition across the endothelium, or lymphocyte trafficking. The main feature of RA that distinguishes it from other arthropathies, such as osteoarthritis, however, is the adhesion of the synovium and subsequent invasion into cartilage and bone. This process is mediated by ‘transformed appearing’ fibroblasts. Although the term ‘transformation’ commonly refers to malignant cells, the term ‘transformed appearing’ does not imply uncontrolled proliferation because RA synovial cells do not reveal an increased rate of proliferation [1], but in this context describes a state of metabolic cellular activation associated with a transformed-appearing cellular phenotype. The mechanisms of the activation of rheumatoid synovial fibroblasts with respect to the overexpression of proto-oncogenes and factors that influence the balance between proliferation and apoptosis are the subject of ongoing research [2]. Invasion and destruction of articular cartilage and bone are due to enzymatic degradation of their matrices, which consist of a variety of structural proteins, such as collagens and proteoglycans, that confer the different biomechanical properties of these tissues. Synovial fibroblasts and chondrocytes produce both matrix-degrading proteases, including metalloproteases and cysteine proteases, and their inhibitors. In disease states, this physiological balance is disturbed by a relative overproduction of proteases; a process which can be induced experimentally by proinflammatory cytokines, such as tumour necrosis factor alpha (TNF-α) and interleukin-1 (IL-1).

All of these pathophysiological features of RA represent potential targets for therapies. Interestingly, the growing body of knowledge concerning the pathophysiology of RA has shed light on the actions of some conventional therapies. Cyclophosphamide and steroids, for example, affect apoptosis, whereas steroids may reduce cytokine synthesis. It is hoped that the development of strategies designed to pinpoint specific pathophysiological targets will result in more effective and specific therapies. Strategies might include, for example, the prevention of further infiltration of inflammatory cells by either interference with leucocyte trafficking through inhibition of neoangiogenesis or inhibition of expression of adhesion molecules. The number and activity of inflammatory cells that have already infiltrated the synovium might be reduced cytotoxically, by the administration of anti-inflammatory cytokines, or neutralization of anti-inflammatory cytokines with antibodies or soluble antigen receptors.

Developments in monoclonal antibody technology rendered the targeting of specific cell types and molecules feasible almost a decade ago [3,4]. Early studies using this technology were driven by the traditional paradigm that T cells are the main instigators of RA and were focused on the depletion of...
T cells. Clinical trials using depleting monoclonal anti-CD4 antibodies in an attempt to reduce the number of CD4-positive T cells in the synovium were surprisingly disappointing. Subsequent trials with other potent T-cell-specific agents, including anti-CD5, CD7, CAMPATH-1 and IL-2/diphtheria toxin fusion proteins, have not shown much better promise. These results may indicate that T cells are effectively depleted in the periphery long before they are reduced in number in the synovium. Alternatively, they may reflect the observation that the disease process is substantially T-cell independent in established RA.

Current efforts are focused on clinical studies using antibodies or soluble receptors for IL-1, IL-6 and TNF-α. The most promising results have been obtained with antibodies against TNF-α, which not only resulted in improvement in the clinical signs and symptoms of articular inflammation, parameters often positively affected in the placebo groups of patients with RA, but also objective laboratory parameters, such as levels of C-reactive protein [5]. Thus, among the proinflammatory cytokines, TNF-α has emerged as probably the most promising therapeutic target. Furthermore, as TNF-α plays a major role in stimulating the expression of matrix-degrading proteases, long-term studies of the effects of antibodies against TNF-α in modifying bone erosion are of particular interest.

Other lines of approach include strategies designed to inhibit synovial proliferation or correct defective apoptosis. Similarly, inhibitors of adhesion might interfere with the adhesion of synovial cells to cartilage and bone. Finally, enzymatic matrix degradation might be reduced by inhibiting the synthesis of metallo- and cysteine proteases or by increasing the availability of specific protease inhibitors either by induction of synthesis or administration of synthetic inhibitors. The latter concept has recently drawn major attention. However, the multiplicity of matrix-degrading enzymes that have been described in the rheumatoid synovium, and the apparent complexity of their physiological and pathophysiological functions, make it important to determine which protease, or set of proteases, to target. Based on their proteolytic activity against constituents of cartilage and bone, the collagens (in particular MMP-1) and stromelysin (MMP-3) and also the cysteine proteases, cathepsins B and L, would appear to be appropriate targets. The first enthusiasm for stromelysin has already been reduced by results obtained with knock-out mice. However, the general concept is supported by several studies in animal models of RA in which the administration of endogenous (e.g. tissue inhibitor of metallo-proteinases) or synthetic inhibitors to mice with collagen II-induced arthritis or rats with adjuvant-induced arthritis has resulted in a decrease in joint destruction and inflammation. Most promising appear so called dual-inhibitors which not only target matrix-degrading metallo-proteinases, but further inhibit the activation of important cytokines such as TNF-α by metallo-proteinases.

The effective application of therapies based on biological agents, such as cytokines, monoclonal antibodies and protease inhibitors is, however, dependent on the resolution of several fundamental problems. These include the bioavailability of the compounds, successful delivery to the target tissues and the achievement of effective concentrations of the agent at the appropriate site, such as the site of matrix degradation. Clinical trials for antibody therapies have revealed further potential problems associated with the systemic administration of peptides, namely the provocation of allergic reactions. This issue has been addressed by the development of so-called chimeric and human engineered antibodies. Antibody therapies, however, require repetitive administrations. Since the modified antibodies also induce neutralizing isotypic or autiodiotypic antibodies, every administration results in less effect for a shorter duration.

The great advances in molecular biology and gene therapy in the past few years have raised hopes that it might soon be possible to deliver specific genes to the synovium [6]. This would permit the production of the biological agents at the site of disease and both optimize the benefits and minimize the side-effects of the therapy.

Clinical trials of gene therapy have been undertaken for several diseases. Initial studies focused on recessive, single-gene disorders, such as cystic fibrosis and Duchenne’s muscular dystrophy, in which the goal is to deliver the normal gene. More recent studies have included attempts to enhance the expression of markers on tumours to permit improved targeting and efficacy of various therapies for malignancies. Unfortunately, gene therapy has not yet been shown to be efficacious in the more than 100 trials that have been conducted to date. The disappointing results are probably due to the low efficiency of the gene transfer systems and the short duration of expression of the delivered gene. Consequently, investigators are currently attempting to improve the vector systems by combining the higher efficiency of vectors based on adenoviruses and retroviruses with the safety of physical delivery systems based on liposomes and plasmids.

Clinical trials of gene therapy for RA have just been initiated at this time. However, it is not well understood how available techniques are suitable for the stable expression of genes in synovium and, in particular, in synovial fibroblasts. Consequently, in vitro systems and animal models are being used to test the feasibility of the various approaches, which differ basically in two respects. The first concerns the way the gene is delivered, i.e. in vivo to the patient as a whole or ex vivo to cells initially removed from the patient and given back to the patient after gene delivery; the second concerns the site to which the gene product has access, i.e. whether it is a systemic delivery or a local delivery only involving individual joints. We favour an ex vivo approach with local gene delivery, both minimizing the risks due to the presently available viral vector systems and the potential systemic side-effects of the therapeutic agent. Accordingly, we utilize a new established SC1D mouse model in which genetically altered human rheumatoid fibroblasts are co-implanted with human...
cartilage. In this model, we can establish the effects of altering the molecular environment on the pattern of invasion of fibroblasts into cartilage. Such models enable, for example, the maintenance of stable levels of cytokines locally for extended periods of time, and thus mimic physiological conditions. In this regard, we have studied, together with Drs C. Evans and P. Robbins, the overexpression of IL-1 receptor antagonist protein (IRAP) [6]. TNF-α receptor p55 soluble protein, as well as IL-10 in this model with distinct results. Although gene therapy for the treatment of RA is still in the early developmental stages, this technology offers unique opportunities to gain further insights into the pathophysiology of the disease. In addition, it offers a valuable tool to evaluate the efficacy and potential side-effects of drugs in animal models.

In summary, based on the above considerations on the molecular and cellular mechanism operating in the pathogenesis of joint destruction in RA, our laboratory is developing novel strategies for inhibiting and/or modulating the following therapeutic targets:

- signalling and transcriptional pathways for synovial cell activation;
- attachment of synovial cells to cartilage and bone;
- production of matrix-degrading enzymes;
- apoptosis of activated synovial cells;
- inflammatory cytokines.

REFERENCES