Molecular therapeutic targets in rheumatoid arthritis

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In an attempt to combat the pain and damage generated by rheumatoid arthritis (RA), new drugs are being developed to target molecular aspects of the disease process. Recently, a major development has been the use of biologicals (antibodies and soluble receptors) that neutralise the activity of tumour necrosis factor α (TNF-α) and interleukin 1 (IL-1), both of which are involved in disease progression. An increase in our understanding of cell and molecular biology has resulted in the identification and investigation of potential new targets, and also the refinement and improvement of current therapeutic modalities. This review describes therapies that are approved, in clinical trials or under pre-clinical investigation at the laboratory level, particularly focusing on cytokines, although other therapeutic targets of interest are mentioned.

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Rheumatoid arthritis

Advances in molecular biology have led to the development of new therapeutics for autoimmune diseases. Rheumatoid arthritis (RA) is one of the commonest autoimmune diseases, affecting 0.5%–1.0% of the adult population of the western world; it has an incidence of about 25 new patients per l00,000 population per annum (Ref. 1). This chronic, systemic inflammatory disease is both debilitating and difficult to manage and leads to a reduced quality of life, irreversible tissue damage, disability and a shortened life expectancy. RA is characterised by polyarticular synovitis, with a prominent immunological, inflammatory and mesenchymal tissue reaction in the synovium, causing pain, swelling and stiffness. The small peripheral joints, such as those in the fingers or wrist, and feet are often the first to be affected by the disease, and the distribution of affected joints is often symmetrical. However, the disease may affect any synovial joint. Patients who have uncontrolled synovitis may develop erosions along the joint surface (reviewed by Ref. 2).

At the cellular level, RA is characterised by a markedly increased cellularity of the synovial membrane. The infiltration of cells such as macrophages and T cells is prominent, as is the proliferation and expansion of fibroblasts within the synovium. Activation of endothelial cells and neovascularisation is also prominent. Other less abundantly found cell types include B cells and dendritic cells. In contrast to the synovial membrane, the RA synovial fluid is enriched with neutrophils, but macrophages, T cells and dendritic cells are also present. Many of these cells have an activated phenotype, express high levels of human leukocyte antigen (HLA) class II and adhesion molecules, and produce most of the cytokines and chemokines that are known (reviewed by Ref. 3). This process culminates in irreversible damage to cartilage, bone and tendon.

The cause of RA has not yet been identified. Environmental factors such as mechanical stress and cigarette smoking have been shown to have a role in disease susceptibility (Refs 4, 5). Despite suggestions that it might be triggered by viral or bacterial infections, no specific pathogen has been implicated. The treatment of RA has centred on the use of disease-modifying anti-rheumatic drugs (DMARDs). The oldest DMARD is injectable gold, which has been used to treat RA patients since the 1920s, and targets many sites in the immune system (Ref. 6). Current best practice includes the use of methotrexate (MTX) (Ref. 7), which was introduced in the 1950s and has since been shown in many trials to inhibit the progression of erosive disease. The precise mechanism of action of MTX is unknown, although many effects are reported, including the inhibition of DNA synthesis and cell replication (Ref. 8). Recent research suggests that T cells are the main target of MTX (Ref. 9). During the 1990s, specifically targeted biological therapies began to use tumour necrosis factor α (TNF-α) and interleukin 1 (IL-1) as molecular targets for therapy (Fig. 1).

In this review, we describe a range of molecular targets that are currently under investigation for the treatment of RA. The main biological and molecular therapeutic strategies that are being used within the field are discussed, particularly the targeting of cytokines, enzymes and molecules that are involved in cell signalling. Cox-2 inhibitors (cyclo-oxygenase-2 inhibitors) are not discussed as their use has been brought into question recently by the US Food and Drug Administration (FDA) (Ref. 10), after Merck withdrew rofecoxib (Vioxx) from the market. The concerns that were raised related to the safety of these inhibitors, as they increase the risk of heart attack and stroke (Refs 11, 12). The full range of targets is too extensive to cover in detail in this review; some of the more promising therapies that are under development at pre-clinical or clinical trials are discussed.

Molecular targets in RA

Cytokines

Advances in the understanding of the role of cytokines in disease have led to new developments in the treatment of inflammatory diseases. Cytokine activities were first identified during the 1960s (Ref. 13), when it was realised that these small, secreted proteins play a significant role in modulating the immune system and specifically inflammation. Although cytokines appear to have pleiotropic activities that make classification difficult, they are generally either pro-inflammatory (e.g. TNF-α and IL-1) or anti-inflammatory [e.g. IL-10 and transforming growth factor β (TGF-β)] in their actions. Cytokines are produced de novo and generally act at low concentrations over small distances for a short time, stimulating changes in the expression of membrane proteins, proliferation of synoviocytes and secretion of effector molecules. The

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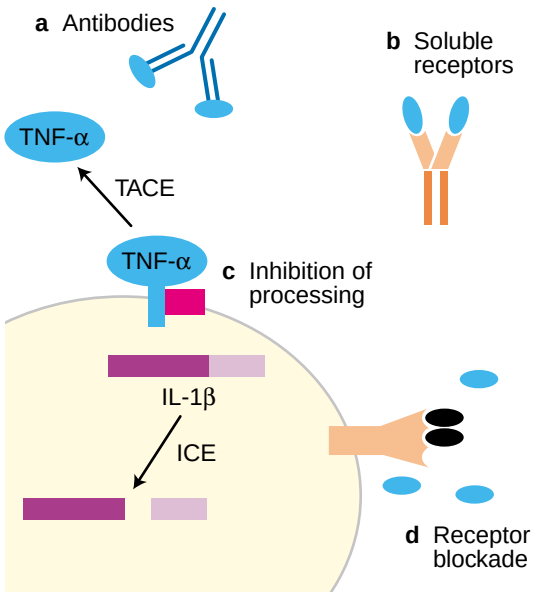

Mechanism of action of biological inhibitors

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Figure 1. Mechanism of action of biological inhibitors. (a) Antibodies are used to inhibit the action of cytokines by binding to them so that they unable to interact with, and activate, the relevant receptor. (b) Soluble receptors act in a similar way to antibodies, by competing with the cell-surface receptors for the cytokine. (c) The enzymatic cleavage of tumour necrosis factor α (TNF-α) from the cell surface requires TNF-α-converting enzyme (TACE), and the cleavage of interleukin-1 β (IL-1β) to produce its active form requires interleukin-1β-converting enzyme (ICE). Cytokines can be inhibited by interfering with their processing, preventing them from being secreted and available for activating receptors. (d) Receptor antagonists bind to the receptor and do not induce the transmission of a signal, thereby blocking cytokines from reaching their target.

involvement of TNF-α, IL-1, IL-6, IL-8, IL-12, IL-15 and IL-18 in RA has been studied extensively (Fig. 2).

Tumour necrosis factor α (TNF-α)

TNF-α is predominantly produced by macrophages but also by other immune cells including lymphocytes, natural killer cells and mast cells (Refs 14, 15). It activates macrophages, endothelial cells, synovial fibroblasts, chondrocytes and osteophytes, stimulating cell proliferation, matrix metalloproteinases (MMPs) and adhesion molecule expression, as well as the release of other cytokines and prostaglandins. TNF-α is found at high concentrations in rheumatoid synovial fluid and synovial tissue and is known to aggravate the damage that is associated with RA (Ref. 16).

A major event in the development of anti-TNF-α as a therapy was the seminal finding by Brennan et al. (Ref. 17) that the neutralisation of TNF-α with antibodies in cultured rheumatoid synovial cells suppressed the expression of other cytokines (e.g. IL-1). This finding was supported by studies with animal models of RA that demonstrated a central role for TNF-α in synovitis and joint destruction: mice that were transgenic for TNF-α or had dysregulated TNF-α production developed arthritis (Refs 18, 19). Two soluble forms of the TNF receptor (TNFR; namely p55 and p75) naturally occur in synovial fluid and can inhibit the action of TNF-α by competing with the cell-surface receptors (Ref. 20). The treatment of mouse models of arthritis with anti-TNF-α antibodies or with soluble TNFR abrogated or lessened the effects of the disease (Refs 19, 21, 22). Based on these observations, anti-TNF-α antibodies and soluble receptors were taken into clinical trials.

Three anti-TNF-α antibody-based therapies are currently being marketed. In 1999, the US FDA granted Centocor (Malvern, PA, USA) approval to use a combination of MTX and a chimaeric monoclonal antibody that binds with high affinity to human TNF-α (Refs 23, 24) to treat RA patients who have responded inadequately to MTX alone. This antibody has shown significant efficacy in trials involving RA patients, and it is now marketed as Remicade® (infliximab) (Ref. 25). Another biological modifier of TNF-α that has been brought to the market is Enbrel® (etanercept), which in contrast to infliximab binds both TNF-α and tumour necrosis factor β (TNF-β). It is a recombinant form of the p75 TNFR and is fused with the Fc region of human IgG_1 (immunoglobulin G_1) to form a dimer (Ref. 26). Recently, a third agent, a completely human anti-TNF monoclonal antibody called Humira® (adalimumab), has entered the market (Ref. 27). As a human antibody, it has the benefit of having a potentially lower immunogenicity combined with a greater therapeutic potential. Infliximab treatment can lead to autoantibodies being generated to double-stranded DNA (both IgM and

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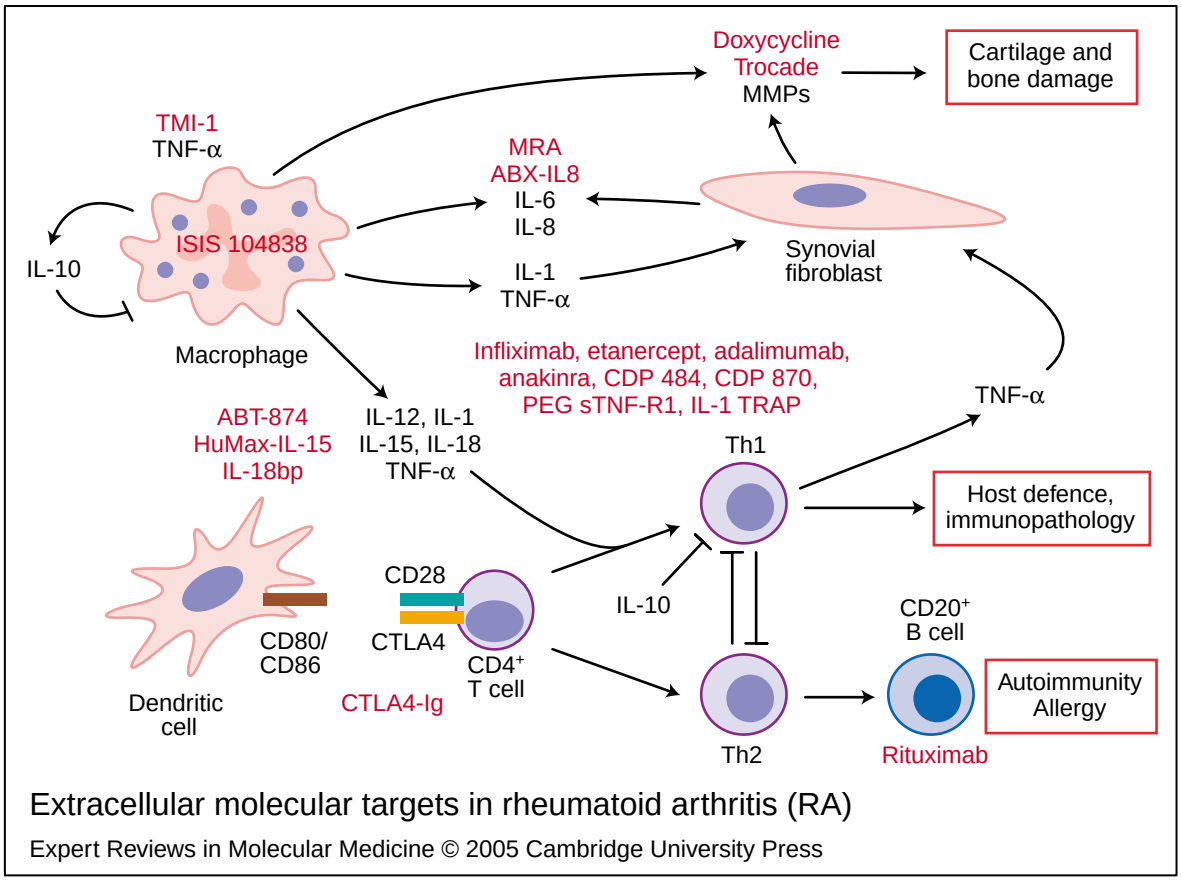

Figure 2. Extracellular molecular targets in rheumatoid arthritis (RA). Therapeutic treatments that are currently available or under investigation for the treatment of RA are shown in red. TMI-1 prevents TNF-α being processed at the cell surface and released as an active soluble form. The largest group of inhibitors are the cytokine inhibitors that act on TNF-α (infliximab, etanercept, adalimumab, CDP 870, PEG sTNF-R1, ISIS 104838), IL-1 (anakinra), IL-6 (MRA), IL-8 (ABX-IL8), IL-12 (ABT-874), IL-15 (HuMax-IL-15) and IL-18 (IL-18bp). The mode of action of such inhibitors includes: as soluble antibodies, as soluble receptors or by direct binding (and blocking) of the receptor. These agents prevent both the stimulation of receptors and the intercellular interactions that these factors induce. Doxycycline and Trocade target the inhibition of MMP-mediated destruction of cartilage and bone. Rituximab depletes the B-cell population, helping to prevent the production of autoantibodies and rheumatoid factors. CTLA4-Ig prevents the receptor interaction between antigen-presenting cells and T cells leading to T-cell stimulation. Abbreviations: CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; IL, interleukin; MMP, matrix metalloproteinase; Th, T helper; TNF-α, tumour necrosis factor α.

IgG class), nucleosome and nuclear antigens (Refs 28, 29). It is used in conjunction with MTX in an attempt to reduce its immunological side effects because MTX has been shown to suppress autoantibodies in lupus erythematosus (Ref. 30), although no such suppressive effect was shown in a recent study of the MTX suppression of autoantibody formation in patients treated with infliximab (Ref. 31). Combined use with MTX potentiates the effectiveness of this and other biologicals, and is the major approach to using these agents.

Other TNF therapies are currently undergoing clinical trials. Celltech has generated a polyethylene glycosylated (PEGylated) humanised antibody fragment that binds with high affinity to TNF-α (CDP 870) (Ref. 32). Initial results from phase III trials have suggested a promising response in RA, with a significant 20% reduction in the American College of Rheumatology score (ACR20) at week 1, which was maintained for the duration of the 24-week study (http://www.medicalnewstoday.com/medicalnews.php?newsid=13761). Compared

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with the current anti-TNF-α therapies, the major advantage of this product is its lower cost of production because synthesis is in a bacterial system. Amgen has developed a PEGylated soluble TNFR type I (PEG sTNF-R1) that has shown efficacy in animal models and is now in Phase II trials (Ref. 33). PEG sTNF-R1 was taken into clinical trial after its efficacy was demonstrated in animal models of RA (Refs 34, 35). ISIS Pharmaceuticals is producing ISIS 104838, an antisense oligonucleotide that reduces the production of TNF-α (Ref. 36). Initial data from Phase II trials have shown a low toxicity, and further trials to determine dose and treatment duration are planned. ISIS 104838 has the potential advantage of fewer side effects and lower production costs, compared with protein-based therapies (see further reading box). However, the efficacy of the systemic use of antisense oligonucleotides is still unclear.

An alternative approach to blocking TNF function has been to prevent the processing of the molecule. TNF-α is synthesised as a membrane-bound protein that is released by enzyme cleavage with TNF-α-converting enzyme (TACE), a member of the MMP superfamily. An inhibitor of TACE, called TMI-1, has been developed (Ref. 37). In experiments on human monocytes, whole blood and human synovial tissue explants from RA patients, TMI-1 inhibited TNF-α secretion (Ref. 37). It has also been shown to be effective at reducing clinical scores in the collagen-induced arthritic mouse (Ref. 37). However, it is unclear what the effect of leaving TNF-α bound to the cell surface will be if this form of the cytokine is still active. Moreover, studies with broad-spectrum MMP inhibitors that block TNF-α release proved ineffective in studies in RA synovial joint cultures (Ref. 38).

Interleukin 1 (IL-1)

IL-1 is a potent inducer of MMPs, eicosanoids, inducible nitric oxide synthase (iNOS) and receptor activator of nuclear factor κB (NF-κB) ligand (RANKL), among many other factors, making it a key pro-inflammatory mediator (the role of IL-1 in RA is reviewed by Ref. 39). It is produced by macrophages and its production is regulated by TNF-α in RA synovium (Refs 17, 40) and, at the local level, IL-1 is a more potent inducer of MMPs than TNF-α. The therapeutic action of TNF biologicals can be attributed to the combined action of decreasing TNF-α but also the resulting decrease of other cytokines such as IL-1 (Ref. 17). Therefore, IL-1 is also a potential therapeutic target in RA.

IL-1 was the first cytokine to be identified in the synovial fluid of RA patients (Ref. 41) as contributing to the progression of inflammation and joint damage associated with RA. In the mid-1980s, a naturally occurring inhibitor was identified, namely IL-1 receptor antagonist (IL-1RA) (Ref. 42). IL-1RA specifically blocks the effects of IL-1 without affecting TNF-α by binding the cell-surface receptor IL-1R1 and preventing activation by interleukin-1 β (IL-1β). IL-1RA is also present in RA synovial fluid (Refs 43, 44) but it appears that, in the disease state, there is an imbalance between IL-1 and IL-1RA. In an attempt to redress this imbalance, a recombinant non-glycosylated form of IL-1RA (Ref. 45) was tested in clinical trials (Refs 46, 47). It proved effective and was marketed as Kineret® (anakinra) in 2001. Approval was given for treating the symptoms and joint destruction associated with RA. However, post-marketing surveillance has shown it to be much less effective than anti-TNF-α biologicals. The reason for this is unclear: it may be that IL-1 is not a potent target in RA or that the agent itself has poor pharmacology. It has a short half-life of 4–6 hours and is slower acting than the TNF biologicals (Ref. 47). Patients can undergo months of daily injections before any reduction in clinical disease activity is observed.

To address the poor efficacy of IL-1RA, a new approach to inhibiting cytokines is being used for IL-1. A high-affinity blocker termed IL-1 TRAP, an engineered protein comprising the Fc region of IgG_1 linked to two signalling chains of the IL-1R, allows binding of IL-1 with high affinity. IL-1 induction of IL-6 was measured in vivo in mice injected with human IL-1β followed either by IL-1 TRAP or IL-1RA. IL-1 TRAP was far more effective at inhibiting IL-6 release (effectively neutralising the action of IL-1) compared with IL-1RA (Ref. 48), making it a good candidate for clinical trials. Regeneron Pharmaceuticals has since confirmed favourable clinical activity and safety/tolerability in a Phase II clinical trial involving RA patients and is planning to start a Phase IIb trial in the near future. This type of technology offers interesting new therapies for other cytokines involved in RA that have not been effectively targeted yet. Celltech has developed CDP 484, a PEGylated antibody fragment against IL-1β. A Phase I trial was scheduled in 2003 but

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no results have been published (see further reading box).

Caspase I [interleukin-1 beta converting enzyme (ICE)] is another possible target aimed at decreasing the amount of IL-1 in RA, as it cleaves the precursor form of IL-1β, changing it to the mature active form. Vertex and Aventis developed a caspase 1 inhibitor, called Pralnacasan (HMR 3480/VX-740) (Ref. 49), but discontinued its Phase IIb trial after adverse toxicology results were received from a long-term animal study, although shorter trials are still being carried out.

Two soluble forms of the IL-1R have been found in synovial fluid that bind IL-1β, competing with the cell-surface receptors for IL-1 (Ref. 50). The approach of using soluble receptors to decrease the availability of a cytokine has been used for TNF and has proved beneficial in RA, but has not yet been developed as an approach for reducing IL-1 levels.

Interleukin 6 (IL-6)

IL-6 is another cytokine that is found in abundance in both the serum and synovial fluid of patients with RA (Refs 51, 52, 53). IL-6 is produced by macrophages, monocytes, T lymphocytes, endothelial cells and synovial fibroblasts. The overproduction of IL-6 in RA might result in the production of autoantibodies owing to the differentiation of B cells and activation of autoreactive T cells (Ref. 54). IL-6 also activates osteoclasts, resulting in bone reabsorption (Ref. 55), upregulates intercellular cell adhesion molecule 1 (ICAM-1) expression (Ref. 56) and is involved in the recruitment of immunocompetent cells into inflammatory tissue, among other effects. The importance of IL-6 in arthritis can also be seen from in vivo experiments in which IL-$6^{-/-}$ mice were backcrossed with mice that were susceptible to antigen-induced arthritis. The IL-$6^{-/-}$ knockout mice only developed mild arthritis, whereas the wildtype mice developed severe arthritis (Ref. 57).

Roche in collaboration with Osaka University has developed a humanised anti-human IL-6R monoclonal antibody (MRA) (Ref. 58). It was developed from the initial mouse anti-IL-6R monoclonal antibody (PM-1), which caused patients to generate antibodies to mouse immunoglobulins. An initial pilot study suggested that MRA was a safe and effective treatment for RA (Ref. 59). Tests were therefore continued to the level of Phase II trials, and again the results were positive: a clear dose–response relationship and good tolerance of the antibody were demonstrated (Ref. 60). MRA has entered into a Phase III trial in Japan, and similar trials are planned for Europe and the USA.

Neutralisation of the receptor may have added benefits in the case of the IL-6 system. The IL-6R can exist in a soluble form that is capable of binding to its ligand. This complex can then interact with the second chain of the IL-6R complex, gp130, and signal, therefore activating cells that may not normally have the entire complex fully expressed.

Interleukin 8 (IL-8)

IL-8 has been found at increased levels in RA (Ref. 61), and is a potential therapeutic target in inflammatory diseases. Synovial fibroblasts, macrophages, endothelial cells and chondrocytes can all produce IL-8. An antibody to IL-8 has been shown to reduce joint swelling significantly in rabbits with monosodium-urate-crystal-induced arthritis (Ref. 62). Abgenix has completed a double-blind Phase IIa trial in RA patients using a human monoclonal antibody targeting IL-8 (ABX-IL8). However, the efficacy was disappointing and there are no further plans for clinical development (see further reading box). Phase IIa and IIb trials with ABX-IL8 were also performed in patients with moderate to severe psoriasis and chronic obstructive pulmonary disease (COPD), respectively, but these trials also proved unsuccessful (see http://www.bioportfolio.com/news/btech_051502_1.htm).

Interleukin 12 (L-12)

IL-12 is a potential target in RA as it has been found in elevated levels in the synovial fluid of RA patients (Ref. 63). It is mainly produced by macrophages and dendritic cells. Experiments using an anti-IL-12 antibody have shown promising results in arthritis mouse models. In one study, an IL-12 antibody prevented the development of collagen-induced arthritis (CIA) in interferon γ (IFN-γ) receptor knockout mice (Ref. 64). IL-12 antibody has also been reported to act in synergy with anti-TNF-α antibodies to inhibit the progression of CIA in mice, producing a greater effect than anti-TNF-α alone (Ref. 65). IL-12 p40 has been shown to be shared with IL-12 and IL-23 (Ref. 66); thus, it is not clear whether

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these results in animal models were due to blockade of the action of either IL-12 or IL-23.

Collaboration between Cambridge Antibody Technology and Abbott has produced a human anti-IL-12 monoclonal antibody called ABT-874 (formerly J695), which has proved to have some potential for treating Crohn's disease and multiple sclerosis. A multi-centre, dose-randomised, double-blind, placebo-controlled study of ABT-874 is currently in progress to test its potential for treating RA (see further reading box).

Interleukin 15 (IL-15)

IL-15 has been detected in RA joint synovium (Ref. 67). It is produced by monocytes and a variety of other cells. IL-15 activates T cells and promotes the release of more IL-15 and stimulates macrophages in a cell-contact-dependent manner to release TNF-α. Pre-clinical data have suggested that a soluble fragment of IL-15Rα may be useful as a therapeutic; when this fragment was administered to DBA/1 mice, it profoundly suppressed the development of CIA (Ref. 68). A human monoclonal antibody against IL-15 (HuMax-IL-15) has been tested in a Phase II trial for RA by Genmab and Amgen. The antibody was found to be safe (with no dose-limiting toxicity) and well tolerated by the patients. The results showed HuMax-IL-15 to be more beneficial than a placebo in patients who had previously failed to respond to treatment with DMARDs (Ref. 69).

Interleukin 18 (IL-18)

IL-18 was originally identified as an IFNγ-inducing factor (Ref. 70). It is mainly produced by macrophages and is closely related to IL-1α, and IL-1β. IL-18 is capable of enhancing the production of IL-1 and TNF, and works in synergy with IL-12 and IL-15, which are both present in the synovium, to increase the production of other cytokines (Ref. 71). Elevated levels of IL-18 have been observed in RA synovial fluid (Ref. 72). A naturally occurring inhibitor to IL-18 is IL-18-binding protein (IL-18bp), a molecule that binds IL-18 in the fluid phase and prevents it from binding to cells. It is similar to the naturally occurring receptor but, instead of being bound to the cell surface, it is a secreted protein (Ref. 73).

Pre-clinical data have suggested that the development of IL-18bp might produce a beneficial therapy for RA. In the murine CIA model, mice infected with an adenovirus expressing the murine gene encoding IL-18bp isoform c showed less severe inflammation or bone erosions in their joints than mice not expressing IL-18bp (Ref. 74). The pharmaceutical company Serono has put an IL-18bp (Tadekinig-α) into a Phase IIa trial for RA, the results of which are awaited.

Matrix metalloproteinase (MMP) inhibitors

The MMPs are a family of 25 zinc- and calcium-dependent proteinases that are involved in the degradation of the extracellular matrix (Ref. 75). MMPs degrade bone and cartilage in the RA joint, although which members of the MMP family are responsible is not known. Tissue inhibitors of metalloproteinases (TIMPs) occur naturally and regulate the activities of MMPs. A balance between MMPs and TIMPs is essential for the normal turnover of extracellular matrix components (Ref. 76). Low-molecular-weight molecules that bind to zinc or other parts of the catalytic site of MMPs have been pursued as inhibitors. So far, clinical trials of these inhibitors have been cut short owing to complications. The broad-range MMP inhibitors batimastat (MB94), marinastat (BB 2516) and CG 270323A are used to treat cancer patients but have all been ruled out as treatments for RA, because trials with marinastat revealed a drug-related toxicity causing upper-body musculoskeletal pain and stiffness of the joints that spread in a time-dependent manner but was reversible on withdrawal of the drug (Ref. 77).

Trocade (Ro 32-3555), an oral MMP-1 inhibitor developed by Roche, appeared to be a strong candidate for testing in clinical trials after it was shown to be a potent inhibitor of cartilage resorption in vitro and in vivo, acting as a collagenase inhibitor (Ref. 78). However, despite Trocade being well tolerated by patients (Ref. 79), trials were discontinued after one year because its efficacy was limited (Ref. 80). This raised questions as to whether the drug had reached the joint or whether the wrong MMP was being targeted.

Currently, the class of antibiotics known as tetracyclines are the only form of treatment in clinical use against MMPs, and the tetracycline doxycycline has been shown to inhibit the activity of some MMPs (Ref. 81). Although antibiotics seem to have a beneficial effect for the treatment of RA (Ref. 82), the tetracyclines can induce lupus (Ref. 83). Thus, although targeting MMPs could theoretically be beneficial in RA, it is clear that a

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new approach to inhibiting these proteases needs to be developed.

Nuclear factor κB (NF-κB)

NF-κB proteins are a family of transcription factors that play an important role in several physiological processes including cell survival, proliferation and activation. The NF-κB family comprises five members, relA (p65), relB, c-Rel, p105/p50 and p100/p52, all of which share the Rel homology domain that allows their dimerisation and translocation to the nucleus. NF-kB dimers are bound to inhibitors of NF-κB (IκB) proteins, which retain NF-κB in the cytosol. In the so-called canonical or classical activation pathway, inflammatory mediators such as TNF and IL-1, activate IκB kinase 2 (IKK2) within the multisubunit IKK complex, which in turn phosphorylates IκB inducing its ubiquitination and degradation by the proteasome, releasing NF-κB to translocate to the nucleus (Ref. 84). An alternative or non-canonical pathway of NF-κB activation, under the control of NF-κB-inducing kinase (NIK) and IKK1, has also been described. In response to stimuli such as lymphotoxin beta and CD40L, NIK has been shown to activate IKK1, leading to inducible processing of p100 with preferential nuclear translocation of p52-RelB dimers (Ref. 85).

Once activated, NF-κB is a transcription factor that regulates many inflammatory mediators, including cytokines, chemokines, adhesion and co-stimulatory molecules, major histocompatibility complex (MHC) class I and II antigen-presenting molecules, enzymes and anti-apoptotic proteins (Ref. 86). In RA, NF-κB appears to be activated and localised in the nucleus of both macrophage- and fibroblast-like synoviocytes from both early and later stage patients (Refs 87, 88, 89). NF-κB can promote joint destruction by inducing osteoclast maturation and increased bone-resorbing activity (Ref. 90), and by inhibiting chondrocyte differentiation and the repair of damaged cartilage tissue (Refs 91, 92).

The inhibition of NF-κB through the overexpression of IκBα in RA synovial membrane cultures downregulates the expression of pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6 and IL-8 (Refs 93, 94, 95) without major effects on the expression of anti-inflammatory mediators such as IL-1RA, IL-10 and IL-11 (Ref. 94). NF-κB inhibition also results in the downregulation of MMP 1 and MMP 3 without affecting the beneficial expression of TIMP 1, the natural inhibitor of MMPs. In animal models of arthritis, NF-κB inhibition has a beneficial effect (Refs 96, 97, 98, 99), further supporting NF-κB as a potential therapeutic target in RA.

One strategy to block NF-κB activation involves targeting the 26S subunit of the proteasome, thus inhibiting IκBα degradation, NF-κB nuclear translocation, as well as preventing inducible p100 NF-κB processing (Fig. 3). Interestingly, one such proteasome inhibitor, bortezomib (Velcade; Millennium), had a fast-track clinical development and has recently been approved by the FDA for the treatment of multiple myeloma and is under development for various other haematological malignancies. Nonetheless, it is not clear whether the therapeutic effects of bortezomib are due to the inhibition of IκBα degradation (and NF-κB activation) or to the inhibition of other targets. Moreover, in chronic inflammatory diseases such as RA, the side effects of bortezomib may not be acceptable for longer term treatment. Thus, the most promising approach to block NF-κB specifically appears to be through the targeting of IKK2, which phosphorylates IκBα, allowing it to be degraded. Although in RA synovial membrane cultures, the inhibition of IKK2 only marginally affects TNF-α production, it has profound inhibitory effects on the expression of most other cytokines [e.g. vascular endothelial growth factor (VEGF), IL-1β, IL-6, IL-8] and MMPs, and also inhibits the activation of the endothelium (Ref. 100). IKK2 inhibitors that are currently under development have been recently reviewed elsewhere (Ref. 101).

Mitogen-activated protein kinases (MAPKs)

The MAPKs are a group of related kinase proteins that require dual phosphorylation of tyrosine and serine/threonine (Ref. 102). The three major ones are p38, p42/44 (ERK) and p46/54 (JNK), which are activated by a kinase cascade. Activated p38, p42/44 and p54 MAPKs are all present in synovial tissue from RA patients (Refs 103, 104). p42/44 MAPK activation is localised around the synovial microvessels, p54 MAPK activation is found around and within the mononuclear cell infiltrates, and p38 MAPK activation is mostly seen in the synovial lining layer and in synovial endothelial cells (Ref. 104). The importance of p38 MAPK in inflammation was demonstrated by the

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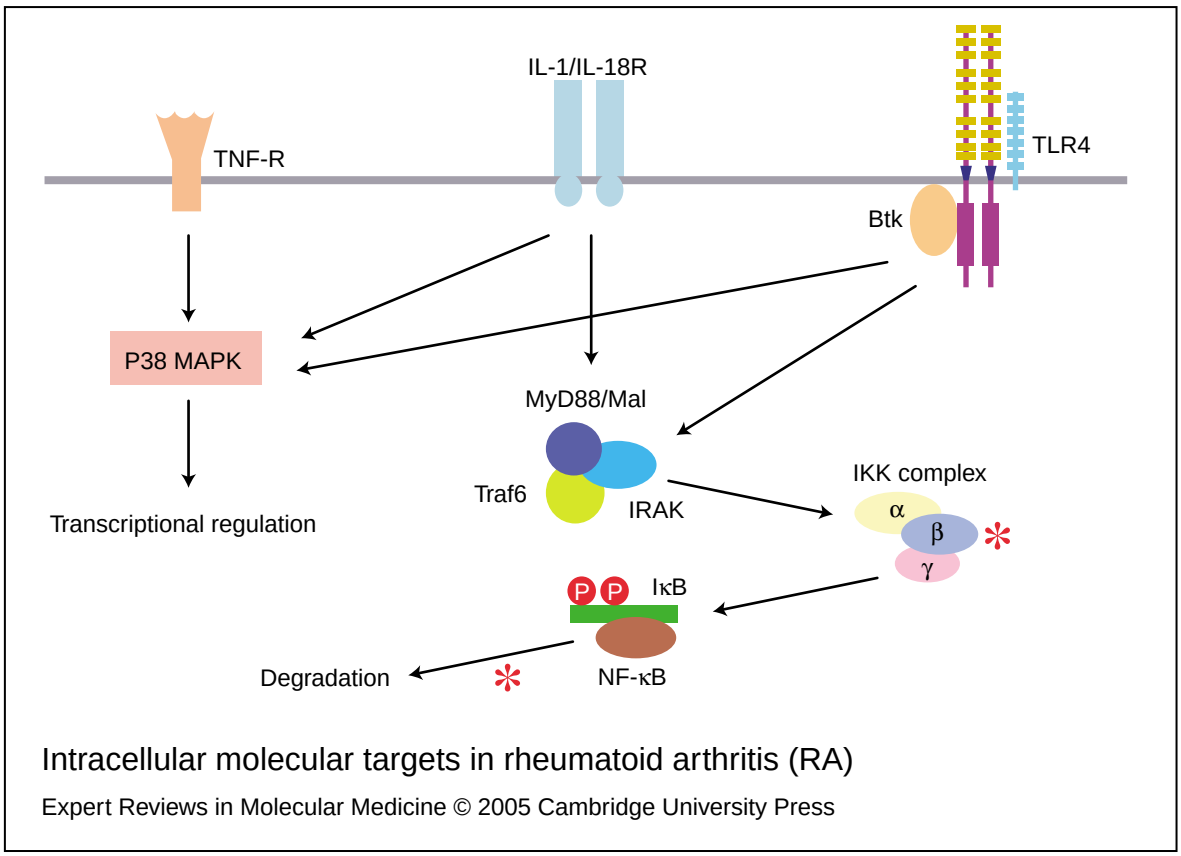

Figure 3. Intracellular molecular targets in rheumatoid arthritis (RA). Both the interleukin 1/18 (IL-1/IL-18) family and the Toll-like receptor family can activate a pathway involving MyD88 (myeloid differentiation primary response gene 88), Mal (MyD88-adapter-like), IRAK (IL-1R-associated kinase) and Traf6 (TNF receptor-associated factor 6) that activates the IκB kinase (IKK) complex and then nuclear factor κB (NF-κB). The activation of NF-κB in RA by this pathway can potentially be inhibited at two points, each marked with a red asterisk: kinase inhibitors can be used to inhibit IKKβ or proteasome inhibitors (bortezomib) can be used to block the degradation of IκB and the subsequent activation of NF-κB. Btk (Bruton tyrosine kinase) has also proved to be a potential target in RA and is known to activate p38. Inhibitors of Btk are under development. TNF-R (tumour necrosis factor receptor), IL-1/IL-18 receptors and Toll-like receptors can all activate p38 MAPK (mitogen-activated protein kinase) through a cascade of kinases leading to transcriptional regulation of inflammatory factors. Inhibitors of p38 MAPK are under investigation at both the laboratory level and at the clinical level. Abbreviation: P, phosphorylation.

discovery that the inhibition of this enzyme had a profound effect on TNF-α production in lipopolysaccharide (LPS)-stimulated macrophages (Refs 105, 106, 107). The other MAPKs do not appear to have such a central role in TNF-α production, although a role has been reported. In human monocytes/macrophages, p54 MAPK (JNK) has been proposed to control TNF-α production at the translational level (Ref. 108), whereas p42/44 MAPK (ERK) affects TNF-α production at the transcriptional level (Refs 107, 109). The expression of other inflammatory cytokines such as IL-1, IL-6 and IL-8 is also regulated by MAPKs (Refs 105, 106, 110).

In mouse and/or rat models of arthritis, p38 MAPK inhibitors such as SB 203580 (Ref. 111), SB 220025 (Ref. 112), SB 242235 (Ref. 113), RWJ 67657 (Ref. 114) or RPR200765A (Ref. 115), some of which are also orally effective, reduce the incidence of arthritis and ameliorate established disease. By contrast, the p54 MAPK inhibitor SP600125 prevents radiological joint destruction but only modestly decreases paw swelling in mouse arthritis (Ref. 116).

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To our knowledge, there are no inhibitors of ERK or JNK in clinical trials. The situation with p38 MAPK inhibitors is quite different. Because the chemical inhibition of p38 MAPK demonstrated the importance of this enzyme to TNF-α synthesis (Ref. 117), the p38 MAPK has been seen as a key target for the treatment of RA (Fig. 3). However, despite a decade passing since these original findings, no inhibitor of p38 MAPK has moved beyond Phase II trials. So far, toxicity has been a problem but seems to be related to the chemistry of the inhibitors rather than to their mode of action.

Phosphodiesterase (PDE) inhibitors

The PDE-4 enzyme inactivates cAMP and is expressed in inflammatory cells such as monocytes and dendritic cells. Inhibitors of PDE-4 are useful in controlling inflammation because they bring about a sustained elevated level of cAMP that leads to activation of protein kinase A (PKA) and subsequent inhibition of transcription factors like NF-κB that transcribe inflammatory genes (e.g. TNF-α).

The main areas of investigation for PDE-4 inhibitors have been in the treatment of COPD and asthma (Refs 118, 119). PDE-4 inhibitors have proved to have a therapeutic benefit in animal models; one inhibitor, rolipram (manufactured by AG Scientific), has proved beneficial in a mouse model of asthma, where the mice were sensitised and then re-exposed to ovalbumin (Ref. 120). Rolipram has also been tested in a rat arthritis model where it was observed to have anti-inflammatory actions in suppressing TNF-α and inhibition of cellular infiltration, as well as suppressing bone and cartilage destruction (Ref. 121). Rolipram has also been tested in a clinical trial but was found to have dose-limiting side effects of nausea and emesis (vomiting). Another inhibitor, Ariflo (cilomilast) manufactured by GlaxoSmithKline, has also been tested in clinical trials and was given FDA approval for the treatment of COPD.

Daxas® (roflumilast), which is being developed by Altana Pharma, is one of a new generation of PDE-4 inhibitors that are better tolerated and therefore show more potential for clinical approval. Multinational Phase III clinical studies around Europe involving patients who have asthma and COPD have shown positive results (Refs 122, 123). Celgene is also developing a group of PDE-4 inhibitors, the SelCIDs™ (selective cytokine inhibitory drugs), which incorporate the phthalimide fragment of thalidomide. The PDE-4 inhibitors under investigation by Celgene have the advantage of lower emetic effects compared with inhibitors that are currently in trials (see further reading box). The most potent of these inhibitors, CDC-998, was well tolerated at the doses administered in a Phase I clinical trial. There are now plans for a multiple dosing drug trial, although the focus does not appear to be on RA at present.

Cytotoxic T-lymphocyte-associated antigen 4 (CTLA4)

Class II MHC molecules present antigens to $CD4^+$ T cells that activate them, and have been associated with susceptibility to RA (Ref. 124). Activated T cells have also been shown to be present in the RA synovium (Ref. 125). Full activation of T cells requires the activation of CD28 as well as the engagement of the T-cell receptor with an MHC–peptide complex on an antigen-presenting cell.

CTLA4 is transiently expressed on the cell surface of T cells and can bind CD80 and CD86 on antigen-presenting cells as well as CD28 on T cells, but interacts with a higher avidity to CD80 and CD86 than to CD28. CTLA4 blockade of CD28 engagement inhibits the activation of T cells (Ref. 126) and has been suggested to be a useful therapy in RA. Human CTLA4 fused to the constant region of IgG_1, to increase its half-life, has been used in clinical trials involving RA patients. Initial results indicated that Abatacept (CTLA4-Ig) (along with MTX) is a promising therapy for RA, because the trial patients experienced a significant improvement in their symptoms (Ref. 127). A Phase III clinical trial involving RA patients has shown positive results, suggesting that CTLA4-Ig may be useful in the treatment of patients who do not respond well to conventional treatments (see further reading box).

Interleukin 10 (IL-10)

IL-10 produced by monocytes, macrophages, B cells and T cells acts in vitro to decrease the production of pro-inflammatory cytokines and can increase the production of IL-1RA (Refs 128, 129). Utilising IL-10 is a potential therapeutic strategy in RA. Ongoing studies at King's College London are investigating the delivery of a gene encoding IL-10 via a nasal spray (see further reading box) as therapeutic treatment.

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B cells

Mature B cells contribute to autoimmunity by their ability to produce cytokines, present antigens and secrete autoantibodies (Ref. 130). Autoantibodies such as anti-cyclic citrullinated peptide antibodies have become a useful diagnostic tool for RA (Ref. 131). The interest in B cells as a major factor in the pathogenesis of RA has been generated by the success with anti-CD20 antibody in clinical trials. CD20 is a cell-surface marker of B cells that is absent on plasma cells. Targeting CD20 with a chimaeric monoclonal antibody, called Rituxan (rituximab/MabThera), causes B cells to undergo apoptosis and cell lysis via a cytotoxic mechanism that involves the Fc immunoglobulin fragment and complement activation (Ref. 132). Rituximab was licensed for the treatment of B-cell non-Hodgkin's lymphoma in 1997 (Ref. 133). It has been well tolerated by RA patients in clinical trials when given either on its own or in combination with glucocorticoids, MTX or cyclophospamide. The greatest benefit is achieved when rituximab is used in combination with MTX, including in those patients who previously were non-responsive to MTX. In a Phase IIb trial, B-cell depletion was evident for 6 months after two initial infusions of rituximab (Refs 134, 135).

Given the potential success of B-cell-targeted therapy, another B-cell-related target is Bruton's tyrosine kinase (Btk). It is a member of the Tec family and plays an important role in the signalling mechanisms that differentiate pre-B cells into mature B cells (Ref. 136). This was first discovered in X-linked agammaglobulinaemia (XLA) patients who lack Btk (Ref. 137). The targeting of this kinase may be an alternative means of desensitising B-cell signalling, and thus providing a therapeutic effect in autoimmune diseases including RA (Ref. 138). More recently, Btk has been shown to be a key element in the signalling pathways induced in macrophages by LPS stimulation of Toll-like receptor (TLR) 4 leading to production of TNF-α, a key cytokine in RA pathogenesis (Ref. 139). TLRs have been suggested to play a role in RA but the evidence for this is still circumstantial (Ref. 140). Btk also appears to be a proximal regulator of p38 MAPK (Fig. 3) and, because Btk has a much more restricted biological distribution than p38 MAPK, it might represent a more attractive target to inhibit.

Clinical implications

The targeting of any molecule that is integral to the adaptive immune response will always pose a risk of immunosuppression and infections leading to adverse effects. The number of biological treatments available for RA has increased considerably in recent years, and many new products are either in pre-clinical development or undergoing clinical trials (Table 1). Although these treatments have brought hope of new ways to target signalling pathways in human disease, there have been some drawbacks. TNF-α and IL-1 have been the main clinical targets, but these proteins are also major pro-inflammatory cytokines in the role against infection. Inhibiting their effects can therefore increase the risk of infection.

A small number of patients who were treated with anti-TNF-α therapies have experienced a lupus-like syndrome, demyelination syndrome and serious infections including bacterial sepsis and reactivation of latent *Mycobacterium tuberculosis* (reviewed by Ref. 141). The incidence of tuberculosis (TB) in anti-TNF-α-treated patients is approximately 1 in 1000 patient exposures, which in most cases appeared to be due to a reactivation of latent TB (Ref. 142). TNF-α is known to play an important role in host defence against TB in a TNF-α knockout mouse model (Ref. 143). The increased infection risk with the anti-TNF-α therapy infliximab may be due to the reduced IFNγ production that has been observed with this treatment (Ref. 144). INFγ activates phagocytosis and resulted in the killing of intracellular bacteria. Treatment with these anti-TNF-α therapies has also been associated with the production of anti-dsDNA antibodies (Refs 145, 146), but the incidence of lupus in these patients remains rare (Refs 147, 148). Demyelination syndrome has been reported in a few patients but like lupus this occurs very rarely (Ref. 149). There have also been suggestions that TNF blockade can lead to an increased risk of lymphomas (Ref. 150) but at present the evidence is not conclusive. Minor, non-serious, injection-site reactions are common with the anti-TNF-α etanercept treatment, and hypersensitivity to infliximab has been seen in some patients along with the production of antibodies to the drug itself.

With the IL-1RA inhibitor anakinra, the risk of impairment of host defence mechanisms is relatively reduced in comparison with the risks for the TNF biologicals. This may be because IL-1

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Table 1. Summary of rheumatoid arthritis therapeutics in development

Name	Type / Target	Manufacturer	Clinical stage	Refs
Remicade® (infliximab)	Monoclonal antibody / TNF-α	Centocor Inc.	FDA approved	25
Enbrel® (etanercept)	Receptor / TNF-α	Immunex/Wyeth	FDA approved	26
Humira® (adalimumab)	Monoclonal antibody /TNF-α	Abbott	FDA approved	27
CDP 870	Monoclonal antibody /TNF-α	Celltech	Phase III	32
PEGylated soluble TNFR type I	Receptor / TNF-α	Amgen	Phase II	33
ISIS 104838	Antisense oligonucleotide / TNF-α	ISIS	Pre-clinical	36
TMI-1	Small molecule / TACE	Wyeth	Pre-clinical	37
Kineret® (anakinra)	Protein / IL-1	Amgen	FDA approved	46, 47
IL-1 TRAP	Receptor / IL-1	Regeneron	Phase IIb	48
CDP 484	PEGylated antibody fragment / IL-1β	Celltech	Phase I	Further reading box
Pralnacasan	Small molecule / Caspase I / IL-1	Vertex/Aventis	Discontinued after Phase IIb	49
MRA	Monoclonal antibody / IL-6	Chugai/Roche	Phase III	60, 152
ABX-IL8	Monoclonal antibody / IL-8	Abgenix	Discontinued after Phase IIa	Further reading box
ABT-874	Monoclonal antibody / IL-12	CAT/Abbott	Phase II (Phase I/II)	Further reading box
HuMax-IL-15	Monoclonal antibody / IL-15	Genmab/Amgen	Phase II	69
IL-18bp (Tadekinig-α)	Protein / IL-18	Serono	Phase IIa	Further reading box
Trocade (Ro 32-3555)	Small molecule / MMP-1	Roche	Discontinued after Phase I	79
IKK2 inhibitors	Small molecule / IKK2	Various companies	Pre-clinical	Reviewed in Ref. 101
p38 MAPK inhibitors	Small molecule / p38 MAPK	Various companies	Some in Phase I/II; many discontinued	111, 112, 113, 114, 115
Abatacept (CTLA4-Ig)	Fusion protein / CTLA4	Repligen Corporation	Phase III	127
Rituxan (Rituximab/MabThera)	Monoclonal antibody / CD20	Genentech	Phase III	Further reading box

Abbreviations: CTLA4, cytotoxic T-lymphocyte-associated antigen 4; IKK2, IκB kinase 2; IL, interleukin; MAPK, mitogen-activated protein kinase; MMP-1, matrix metalloproteinase 1; TACE, TNF-α-converting enzyme; TNF-α, tumour necrosis factor α.

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works downstream of TNF and has less effect on immunocompetent cells, but injection-site reactions are seen in some patients. No serious opportunistic infections have been reported in RA patients on long-term anakinra treatment (Ref. 151). Another limiting factor of the new biological therapies is that some patients do not show a significant benefit when treated with them.

Concluding remarks

The advances made during the past decade have provided more-effective treatments for RA but improvements are still needed. The development of a more efficacious oral DMARD would be beneficial to avoid injection-site reactions and would be preferred by patients as an easier form of drug administration. As our understanding of signalling pathways in inflammatory cells that are involved in the pathogenesis of RA increases, other more-specific therapeutic targets should come to light that will potentially give beneficial effects to a greater number of patients.

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Further reading, resources and contacts

CDP 484 – the Nektar Therapeutics website provides information on CDP 484 and the company's collaboration with Celltech.

http://www.nektar.com/content/pr_1034957161

ISIS 104838 – a report of the Phase II trial of ISIS 104838 in RA is available on the ISIS Pharmaceuticals website.

http://phx.corporate-ir.net/phoenix.zhtml?c=94554&p=irol-newsArticle&ID=565722&highlight=

ABX-IL8 – the Abgenix and BioSpace websites both give the latest news on ABX-IL8.

http://www.abgenix.com/productdevelopment/?view=DevelopmentStrategy

http://www.biospace.com/ccis/news_story.cfm?StoryID=8750119&full=1

ABT-874 – the University of California, San Diego (UCSD) Center for Innovative Therapy provides information on clinical trials of ABT-874.

http://cit.ucsd.edu/level2/clintri/sumclintrials.htm

Tadekinig-α – the Serono website provides the latest news on Tadekinig-α (IL-18bp).

http://www.serono.com/products/areas.jsp?major=1&minor=4

CDC-998 – the BioSpace website and a meeting report from Advances in Anti-Arthritic Agents both give information on CDC-998:

http://links.biospace.com/news_story.cfm?StoryID=4813304&full=1

Norman, P. (11 July 2002) Advances in Anti-Arthritic Agents – SMi's Third Annual Conference, IDrugs 5, pp. 530–538 (http://www.biomedcentral.com/content/pdf/cd-457688.pdf)

IL-10 – the King's College London website describes a potential IL-10 therapy for RA.

http://www.kcl.ac.uk/phpnews/wmview.php?ArtID=660

CTLA4-Ig – the Biotechnology Healthcare website gives an initial report of Phase III clinical trials.

http://www.biotechnologyhealthcare.com/Daily/DailyDetail.cfm?chosen=406

Rituximab – the Genentech website provides information about Rituximab.

http://www.gene.com/gene/pipeline/status/immunology/rituxan/

Features associated with this article

Figures

Figure 1. Mechanism of action of biological inhibitors.
Figure 2. Extracellular molecular targets in rheumatoid arthritis (RA).
Figure 3. Intracellular molecular targets in rheumatoid arthritis (RA).

Table

Table 1. Summary of rheumatoid arthritis therapeutics in development.

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